STUDIES ON THE DECALIN TYPE SESQUITERPENOID SYSTEM: SYNTHETIC METHODOLOGIES AND APPLICATIONS

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

1985

ACKNOWLEDGEMENTS

The author wishes to express his deepest respect to Dr. M. A. Battiste for his advice, understanding and guidance. He also wishes to express appreciation for aid in the completion of the research to Dr. W. R. Dolbier, Dr. J. F. Helling, Dr. R. W. King, Dr. L. Strekowski, Dr. R. A. Yost and Dr. G. Ritter. The help and friendship received from Dr. R. Wydra, S. Sengupta, S. Yoon, S. Cato, and M. Cuevas made this research more enjoyable and productive. The cooperation of every member of the Organic Division deserves to be acknowledged. Special thanks are given to J. Rocca, Dr. R. Awartani and H. Schultz for spectroscopic data. The author would like to thank S. Ahn for her encouragement, love and help along the way which allowed this work to become a reality.

And lastly, the author wishes to express his gratitude to the Department of Chemistry for financial support.

TABLE OF CONTENTS

		PAGE
ACKNOWLEDGEMENTS		ii
LIST OF TABLES		v
ABBREVIATIONS		vi
ABSTRACT		vii
CHAPTERS		
I	INTRODUCTION	1
II	SYNTHETIC STRATEGY FOR CONSTRUCTION OF trans-DECALIN SYSTEMS: GORGONENE AND SELINENE TYPE SESQUITERPENOIDS	12
	Intermolecular Pathway	15
	Intramolecular Pathway	17
	1,4-Addition to $\Delta^{9,10}$ Decalenone Systems	20
	Studies on the Model Systems: trans-Lactone of 2-Hydroxycyclohex-2-ene Acetic Acid (17).	21
III	RESULTS AND DISCUSSION	23
	Preparation of Starting Material, 3-Vinyl-cyclohex-2-enol (14)	23
	Intermolecular Diels-Alder Reactions of Dienol (14)	24
	Use of Intramolecular Diels-Alder (IMDA) Approach	33
	Studies on the Model System, trans-γ-Lactone cyclohex-4-ene Acetic Acid (17)	39
	Opening of Lactone via Monomethylation	53
	Synthetic Route to α,β-Unsaturated Ketone (27) from the Hydroxyketone (16b)	60
	Conjugate 1,4-Addition to the Sterically Hindered α,β-Unsaturated Decalone System (27)	61

IV EXPERIMENTAL 71

General 71
Spectra 71
Reagents and Solvents 72
Apparatus and Techniques 72

APPENDIX 98

BIBLIOGRAPHY 105

BIOGRAPHICAL SKETCH 110

LIST OF TABLES

Table		Page
1	Synthesis of 3-vinylcyclohex-2-enylpropenoate (18) under various conditions	34
2	Reactions of trans-lactone of 2-hydroxyhex-4-ene acetic acid (17) with methyllithium	41
3	Reactions of lactone (17) with methyllithium in the presence of trimethylsilychloride (TMSCl)	45
4	Reactions of lactone (17) with organocopper reagents	47
5	Reactions of lactone with trimethylsilylmethyl magnesium chloride (Me_3SiCH_2MgCl) in various conditions	50
6	Opening of lactone (15) by various reagents	56
7	1,4-Addition trials on α,β-unsaturated system (27) with homoorganocopper reagents	62
8	1,4-Addition trials on α,β-unsaturated system (27) with heteroorganocopper reagents	65
9	Conversion of α,β-unsaturated decalin systems (27) with various reagents	70

ABBREVIATIONS

Dibal-H	diisobutyl aluminum hydride
DMAP	4-dimethylaminopyridine
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
Et	ethyl
Et_2O	diethyl ether
hr	hour
LDA	lithium diisopropylamide
$LiAlH_4$	lithium aluminum hydride
m-CPBA	meta-chloroperoxybenzoic acid
Mol	moles
Me	methyl
MeLi	methyllithium
Me_2CuLi_2	lithium dimethylcuprate
NEt_3	triethylamine
Nu	nucleophile
Py	pyridine
THF	tetrahydrofuran
TMS	trimethylsilyl
TMSCl	trimethylsilychloride
$TMSCH_2Cl$	trimethylsilylmethylchloride
TsOH	p-toluenesulfonic acid

Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

STUDIES ON THE DECALIN TYPE SESQUITTERPENOID SYSTEM: SYNTHETIC METHODOLOGIES AND APPLICATIONS

By

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December, 1985

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Major Department: Chemistry

The intramolecular Diels-Alder reaction for assembling decalins has found increased application during the last decade. It has the advantage over the intermolecular version with respect to regio- and in some instances stereo-chemical problems in constructing the bicyclic system. Indeed, despite considerable progress, stereospecific olefin synthesis is often more difficult than stereocontrol in cyclic systems.

The object of this dissertation is to investigate another possible approach to decalin type sesquiterpenes which does not utilize the Robinson annelation procedure and which appears to be general for the efficient and stereoselective synthesis for this class of terpenes. The construction of β-gorgonene and β-selinene type bicyclic systems was studied by way of inter- and intramolecular (4 + 2) reactions of the previously unexplored diene system, 3-vinylcyclohex-2-enol.

A major portion of this dissertation is also devoted to problems concerned with the direct conversion of γ-lactones to the corresponding hydroxymethylketones. A model system, the trans-γ-lactone of trans-2-hydroxycyclohex-4-ene acetic acid, was employed in the more general study of reagents and procedures necessary to accomplish this task in one step.

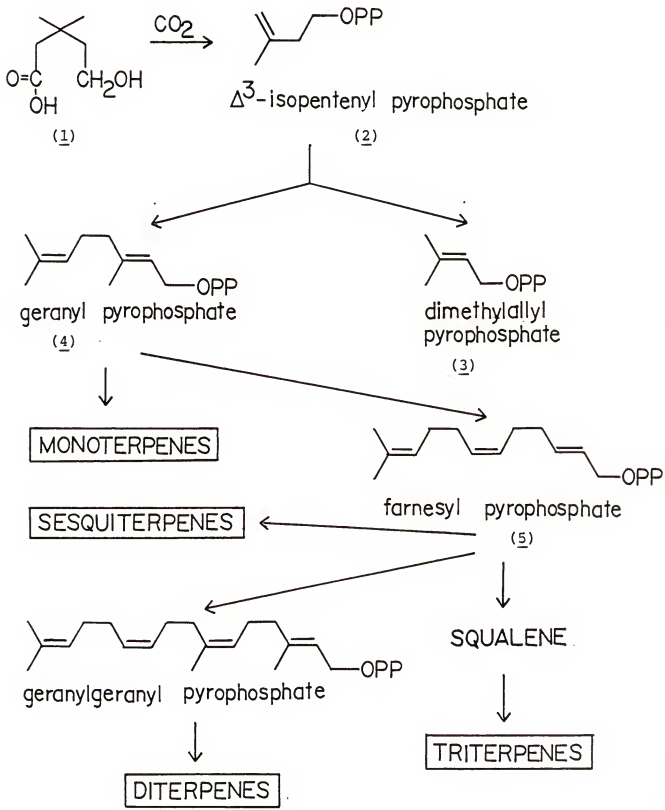
1,4-conjugate addition via organocopper reagent (dimethylcopperlithium) was successful with 8-carbethoxy-1,2,3,4,5,6,7,8-octahydronaphthalen-1-one, but not with 8-isopropenyl-1,2,3,4,5,6,7,8-octahydronaphthalen-1-one. When the reactivity of the organocopper reagent was increased, only 1,2-addition or elimination was observed with the latter.

CHAPTER I
INTRODUCTION

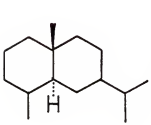
The "isoprene rule" states in principle that the carbon skeletons of a number of naturally occurring compounds, collectively referred to as terpenes, can be divided into distinct isoprenoid units.[1] More recently, with the advent of sophisticated methods of isolation, separation, and structural elucidation, terpene research has expanded greatly and has established these compounds as one of the most diverse and intriguing groups of natural products.

Extensive investigations have demonstrated that mevalonic acid (1) is the primary direct precursor to the isoprene unit.[2] The formation of the isoprene units Δ^3-isopentenyl pyrophosphate (2) and dimethylallyl pyrophosphate (3) from mevalonic acid has been elucidated.[3] Sesquiterpenes originate from farnesyl pyrophosphate (5), a 15 carbon intermediate derived from the union of geranyl pyrophosphate (4) and Δ^3-isopentenyl pyrophosphate (2) as shown in Scheme I.

Scheme 1


CO2
OPP
O=C
CH2OH
OH
(1)
Δ3-isopentenyl pyrophosphate
(2)
OPP
geranyl pyrophosphate
(4)
OPP
dimethylallyl pyrophosphate
(3)
MONOTERPENES
OPP
farnesyl pyrophosphate
(5)
SESQUITERPENES
SQUALENE
OPP
geranylgeranyl pyrophosphate
TRITERPENES
DITERPENES

Among the sesquiterpenes believed to have originated from farnesyl pyrophosphate, the bicyclo[4.4.0] decane framework is found in four main subclasses, the eudesmanes (6), eremophilanes (7), cadinanes (8), and β-gorgonene (9). It is also present in some polycyclic sesquiterpenes.[4]



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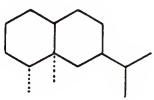

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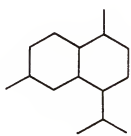

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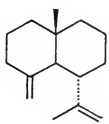


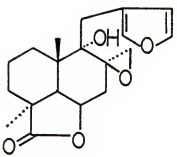
(9)

Prior to 1970, approaches to this angularly substituted decalin nucleus have been based almost entirely on the Robinson annelation methodology.[5] Only recently has a gradual shift towards other methods been observed. The problems associated with the efficiency and the regio- and stereo-control of both steps in this annelation were adequately discussed elsewhere[6] and will not be dealt with, at length, in this dissertation. To construct the bicyclic ring system, it is generally observed that the reaction of cyclohexanone enolates with alkyl vinyl ketones in aprotic medium produces the adducts in low yields because of polymerization of the enone and/or polyalkylation.

Among other methodolgies, the Diels-Alder reaction stands out as one of the most important tools for synthesis of six-membered carbocycles. The intermolecular version[7] for angularly methylated decalins from substituted cyclohexenones as dienophiles has found limited application in the past. However, with improved applications which make use of more reactive dienes or dienophiles as well as catalysts, dramatic increases in yields have been observed in some cases.[8]

The intramolecular Diels-Alder reaction for assembling decalins has found increased application during the last decade. It has advantages over the intermolecular version with respect to regio-, and especially, stereo-chemical problems. Nevertheless, despite considerable progress, stereospecific olefin synthesis may still be more difficult than stereo-control in cyclic systems. Several reports have described the formation of angularly methylated decalin systems.[9a-9d]

One interesting feature of the new sesqui- and diterpenoids described over the past decades is the increasing in number of skeletons based on the tricyclic lactone ring, leonotrinin (10),[10] kaurenolide (11),[11] humirianthenolide (12)[12] and alkavinone (13).[13,14]



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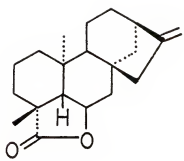

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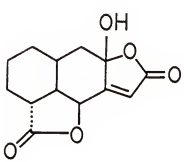

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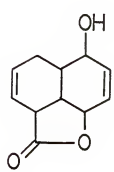
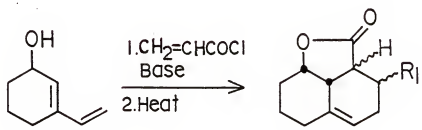


(13)

The object of this dissertation is to develop new and, it is hoped, improved approaches to the main classes of decalin type sesquiterpenes, especially β-gorgonene and β-selinene systems. In selecting material for inclusion, it was not always possible to distinguish new methods or reactions

falling strictly within the scope of the title. Therefore, an attempt has been made to group, in different sections, a number of methods under a common heading.

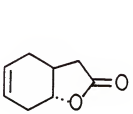
In connection with current synthetic work in this laboratory the construction of β-gorgonene and β-selinene type bicyclic systems by way of inter- and intra- molecular (4+2) cycloadditions of the previously unexplored diene system, 3-vinyl-cyclohex-2-enol (14) was explored. As indicated below this diene affords the possibility of direct entry to the tricyclic lactone skeletal unit common to terpenes 10-13.



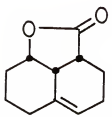
(14)

A major portion of this dissertation is therefore devoted to problems concerned with the utilization of this tricyclic lactone system in sesquiterpene synthesis. Specific points of interest are the problems associated with the direct transformation of γ-lactones such as (15) into the corresponding methyl ketones (16).

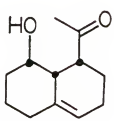
A model system, γ-lactone 17, was primarily employed for these investigations of lactone openings, since it was more readily available[15] and allowed an extension of our basic approach to encompass lactones of less structural complexity.



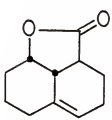
(17)



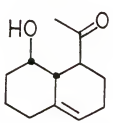
(15a)



(16a)



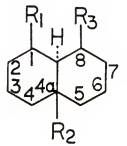
(15b)



(16b)

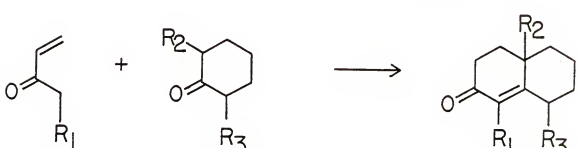
Several factors involved in the preparation of hydroxyketones were to be studied. These include the size and the substitution pattern of the lactone, the nature of the organometallic reagent, the temperature, and the solvent.

The trans-fused decalin system bearing functional groups at C(1), C(4a) and C(8) is a unique structural unit in



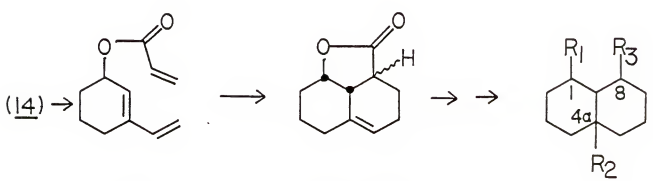
(gorgonene type)

terpenoid and steroid natural products.[16] As mentioned earlier, classical approaches to these subunits via Robinson annelation cannot readily accommodate certain



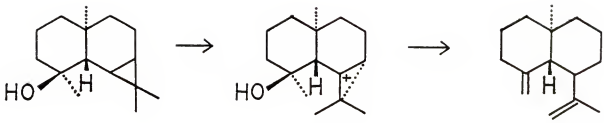
functionality patterns mainly due to steric factors. A complementary strategy for the construction of six-membered rings is based upon the intramolecular Diels-Alder reaction.

A general strategy (Scheme 2) along the lines of the previously suggested intramolecular Diels-Alder reactions of diene ester (18) was conceived for functionalized trans-fused decalins having gorgonene type substitution patterns.



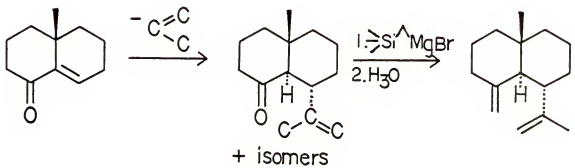
(18) (15a, 15b)

β-Gorgonene (9) is of marine origin and was isolated by Weinheimer et al. (1968)[17] from the red algae Pseudopterogorgia americana. It is the predominant sesquiterpene and occurs along with the maaliene and the aristolenes. An attempt to assess the phylogenetic significance is still premature, but one group[18] has already reported a possible biogenetic type conversion of maaliol (19) to (-)-β-gorgonene by dry HCl, presumably through the corner protonated intermediate (20).



(19) (20) (9)

Diene (9) has an interesting non-isoprenoid type skeleton that violates the usually observed biogenetic substitution pattern. The first and only previous synthesis of gorgonene was reported by Boeckman and utilizes as the key step the Michael type addition of isopropenyl Grignard reagent to enone (21) with copper(I) catalysis.



(21) (22) (9)

The final product, gorgonene (9) was obtained via a Peterson olefination reaction using trimethylsilylmethyl magnesium bromide.

Boeckman's approach to this class of molecules requires that one deal with the problem of stereoselective introduction of the equatorial isopropenyl group. This problem is compounded by the presence of the angular methyl group which exerts a strong steric interaction on the incoming nucleophile at the peri like position in the decalin system. This dissertation investigates other possible synthetic routes which could be applied to many similar terpene skeletons.[19] By contrast the foregoing sequence of Boeckman is limited to construction of the gorgonene type skeleton.

Despite the number of syntheses of eudalene-type sesquiterpenes[19] which have a skeleton similar to that of gorgonene, most of the approaches reported to date have utilized the Robinson annelation sequence to construct the bicyclic skeleton common to this group of natural products.[20,21] In the course of our synthetic studies we have incidentally developed another possible approach to these sesquiterpenes which does not utilize the annelation reaction and which appears to be general for the efficient and stereoselective synthesis of this class of terpenes.

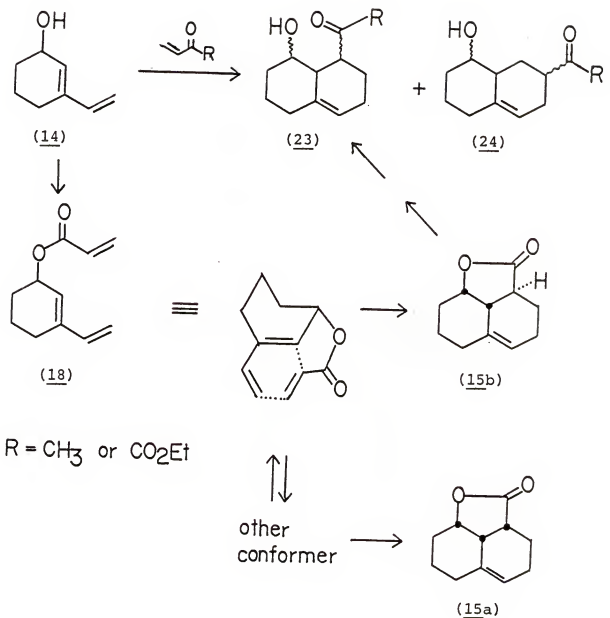
CHAPTER II
SYNTHETIC STRATEGY FOR CONSTRUCTION OF trans-DECALIN SYSTEMS GORGONENE AND SELINENE TYPE SESQUITERPENOIDS

Thermally induced additions of 1,3-diene or 1,3-dipoles to a multiple bond lead to six- or five-membered rings, respectively. These types of cycloadditions involve the simultaneous formation of two sigma bonds, via a highly ordered aromatic transition state.[22] The stereochemical course of this reaction-type is controlled by reactivity and orientation phenomena ascribed to frontier orbital interactions. The great preparative importance of these reactions is shown by the multitude of fascinating applications of the bimolecular Diels-Alder reaction found in the synthesis of complex molecules.

From investigations carried out in recent years it follows that when such cycloadditions are performed in an intramolecular manner, their synthetic potential is substantially increased. Interesting case studies of this reaction are documented in many of the total and partial syntheses reported to date.[23] Intramolecular Diels-Alder reactions provide regiochemical control and may lead to a single stereoisomer being formed exclusively or at least in preponderant amount.

Nevertheless, these reactions can conceivably give rise to a number of stereoisomers depending on geometrical constraints and thermodynamic considerations. As expected the main interaction in the transition state is between the HOMO of the diene and the LUMO of the dienophile. In the usual intermolecular Diels-Alder reaction the orientation of the products obtained from an unsymmetrical diene and an unsymmetrical dienophile is largely governed by the orbital coefficients at the termini of the conjugated system.[24] Thus, vinylcyclohexenol (14) would be expected to afford the two regioisomers (23) and (24) on reaction with methylvinyl ketone or ethyl acrylate (Scheme 3). The lack of regio- and stereo-chemical control in the intermolecular cycloaddition pathway might appear to be a major drawback compared to the intramolecular approach; however, the stereochemical problem can be resolved by introducing sp^2-centers at C-1, C-4a, and C-8a (see Scheme 4). Regioisomer (24) would then provide entry into the eudalene-type sesquiterpene system.[25,26] Thus, there are synthetic advantages for both the inter- and intra-molecular Diels-Alder approaches to the gorgonene as well as the selinene skeletons.

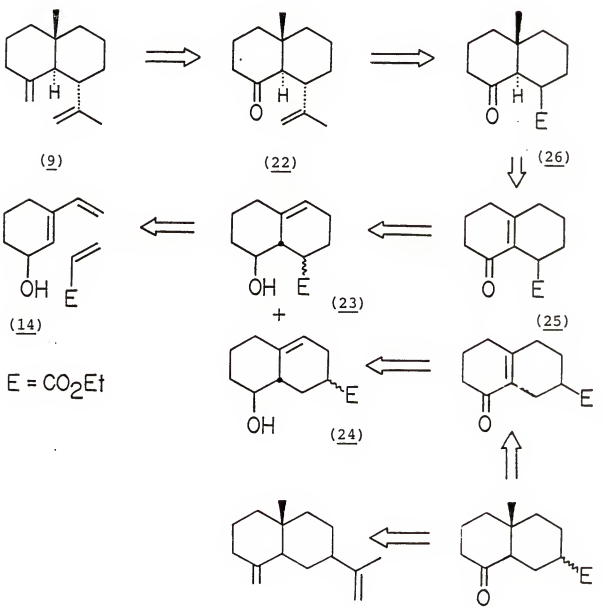
Scheme 3


OH
O
R
HO
O
R
HO
O
R
+
(14)
(23)
(24)
O
O
O
O
H
(18)
(15b)
R = CH3 or CO2Et
other
conformer
O
O
(15a)

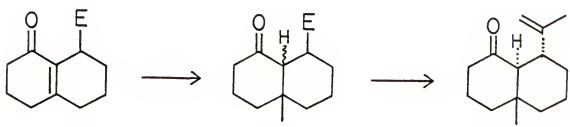
Intermolecular Pathway

The retrosynthetic analysis for β-gorgonene and β-selinene is illustrated in Scheme 4 using ethylacrylate as dienophile. A similar scheme can be written for methyl vinyl ketone as dienophile.

Scheme 4



The detailed chemical procedures shown in Scheme 4 will be discussed in Chapter III. After introducing the angular methyl group at C-4a via 1,4-addition to decalenone (25), the ester and/or other functional groups at C-8 are to be converted into the isopropenyl group.



(25) (26) (22)

In a previous study, directed towards the synthesis of the β-gorgonene type structure, Boeckman and Silver (1975)[27] found that trans-decalone (22) can be obtained by epimerization of the corresponding cis-fused isomer (22a) with methanolic $NaOCH_3$ at room temperature, this procedure affording an equilibrium mixture of trans to cis in a ratio of 7:3. In contrast to this method it was our intention to achieve the equilibration to the trans-decalin with the compound (26).

Intramolecular Pathway

Within certain limitations, the intramolecular strategy[28,29] should afford a somewhat shorter and more efficient entry to the desired gorgonene skeleton via the tricyclic lactone previously discussed.

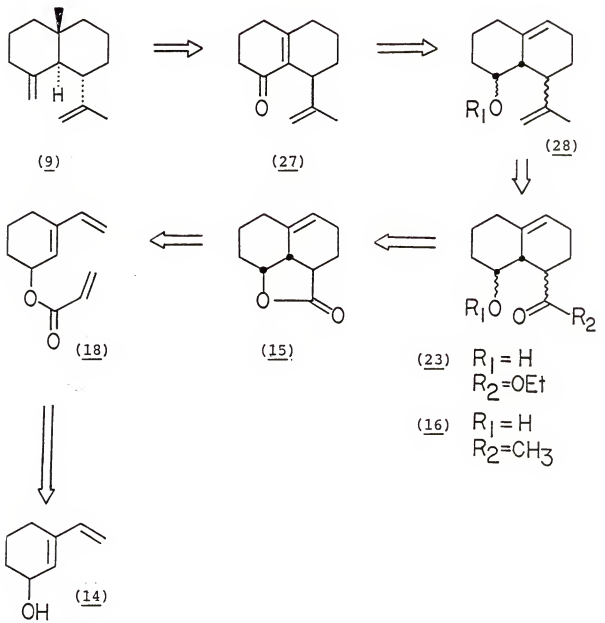
Retrosynthetic analysis is shown for β-gorgonene using lactone (15) as the key intermediate (Scheme 5).

One of the major problems associated with the transformation of γ-lactones such as (15) into the corresponding methyl ketones (16) using methyllithium has been the competing formation of the tertiary alcohol.[30]

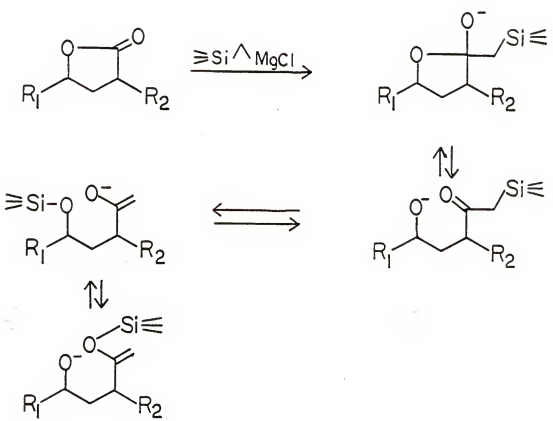
Originally, our strategy called for the preparation of hydroxyketone (16) from the carboxylic acid according to the procedure of Rubbotom;[31] however, difficulties in his method suggested that it would be easier for us to obtain the desired hydroxyketone (16) directly from lactone (15). Furthermore, a report by Jorgensen,[32] showed that a similar decalin carboxylic acid could not be converted to the methyl ketone under a variety of conditions. This may be attributed either to steric factors, or the insolubility of the lithium carboxylate.[32] Therefore direct conversion of the γ-lactone (15) to the hydroxyketone (16) was considered necessary, and our venture into this problem will be described in Chapter III. Our main strategy was to minimize the possible second attack from the nucleophile through an enolization process shown in Scheme 6 using a model lactone system.

Scheme 5

Intramolecular pathway (retrosynthesis)



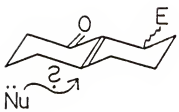
Scheme 6



1,4-Addition to $\Delta^{9,10}$ Decalenone Systems

α,β-Unsaturated carbonyl compounds react with most types of organocopper reagents in a conjugate manner to afford a product in which the new carbon-carbon bond has been formed β to the carbonyl group. Organocopper conjugate addition is therefore like the Michael type reaction of enolate ions with unsaturated carbonyl compounds in terms of the position of the new carbon-carbon bond and in terms of sensitivity to steric factors in the carbonyl compound.

Despite substantial efforts since 1965, the detailed mechanism of organocopper addition and substitution reactions remains uncertain. Most of the literature on copper reagents deals with the effects of the α and β substituted molecules, not the steric or electronic effect on oxygen. Even though it is generally recognized that α,α- and β,β-disubstituted α,β-unsaturated carbonyl compounds react with copper reagents slowly,[33] there remained a question whether this reaction would succeed with (24) as a substrate, due to the severe 1,3-nonbonded-interaction of the incoming reagent with the ester or isopropenyl groups already present.



This idea was speculative since the literature contained no reports of conjugate additions of this decalenone system where carbonyl oxygen is severely hindered.

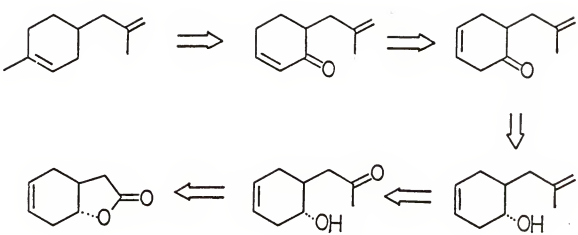
Studies on the Model System: trans-Lactone of 2-Hydroxycyclohex-4-ene Acetic acid (17)

Preliminary research was conducted with the structurally simplified lactone (17) which was readily available from malonate anion opening of the monoepoxide of 1,4-cyclohexadiene.

Opening of the lactone with nucleophile reagents, equilibration to α,β-unsaturated ketones, Wittig type reactions, 1,4-additions and oxidations which are necessary to complete the desired synthesis were studied with this simpler molecule. This synthetic route also can be applied to make a bisabolene type terpene.

The retrosynthetic scheme for these model studies is shown in Scheme 7.

Scheme 7

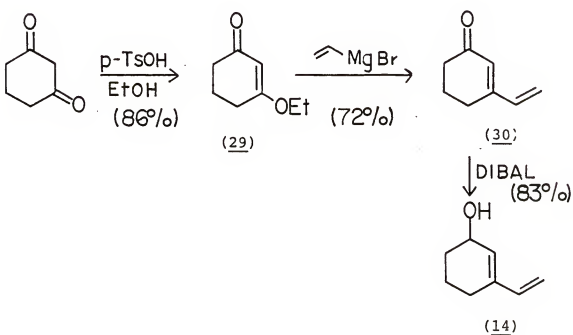


CHAPTER III
RESULTS AND DISCUSSION

The total synthesis of (±)-β-gorgonene was attempted according to the intermolecular and intramolecular Diels-Alder pathways outlined in Schemes 4 and 5 of Chapter II. Each of the major synthetic operations for the two retrosynthetic plans is discussed in the following sections.

Preparation of Starting Material, 3-Vinylcyclohex-2-enol (14)

The alcohol (14) was synthesized in three steps from commercially available dione.



Refluxing 1,3-cyclohexanedione in ethanol in the presence of a catalytic amount of p-toluenesulfonic acid resulted in an 86% yield of ethoxycyclohexenone (29).[34] The crude product was distilled with a short Vigreux column under reduced pressure to produce a colorless oil as the pure compound.

Vinylcyclohexenone (30) was next produced by addition of vinylmagnesium bromide to (29) followed by acidic work up step. Capillary G.C. analysis showed only one major component for the product (30). Dienone (30) was unstable and quickly polymerized at room temperature; thus it was not purified. Instead the crude product was converted directly into vinylcyclohexanol (14) using isobutylaluminium hydride (DIBAL) in ether with 83% yield.

Intermolecular Diels-Alder Reactions of Dienol (14)

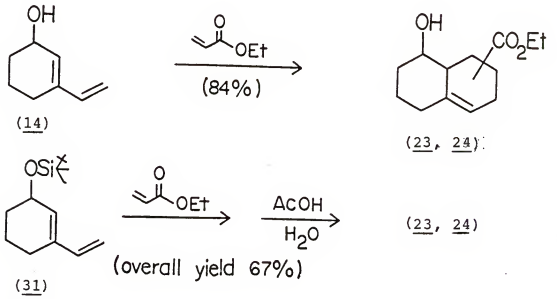
With the aim of investigating the effect of steric and electronic factors in the diene and dienophile on the ratio of the resulting regioisomers, we studied the Diels-Alder condensation of ethyl acrylate and methyl vinyl ketone with the vinylcyclohexenol (14).

All of the trials were carried out under standard conditions by heating a 1:3 mixture of the components at 90-100°C. for 24 hours in the presence of 1-2% hydroquinone or 2,6-di-tert-butyl-4-methylphenol as a polymerization inhibitor.

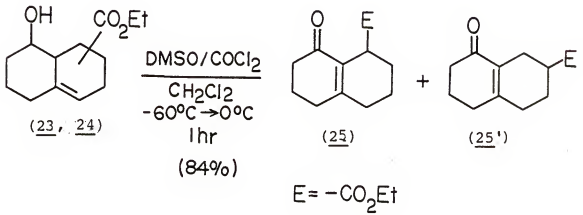
Ethyl acrylate as dienophile

Vinylcyclohexenol (14) was heated with 3 equivalents of ethyl acrylate as described above and after removal of excess dienophile the crude product was chromatographed on silica gel to remove polymeric material. The resulting oil showed 4 major components, corresponding to the isomeric hydroxyester (23) and (24), on capillary G.C. analysis (Crosslinked Silicate column). The crude mixture of esters was used in the subsequent oxidation step without further purification. Determination of the ratio of the regio-isomeric esters (1,3- and 1,4-adducts) was readily accomplished after introduction of the three sp^2- carbon centers in the next synthetic step.

1-tert-Butyldimethylsiloxy-3-vinylcyclohex-2-ene was also treated with ethyl acrylate using the same procedure as above in order to examine hydrogen bonding and steric effects of the oxygen substituents on the regioselectivity of the addition.



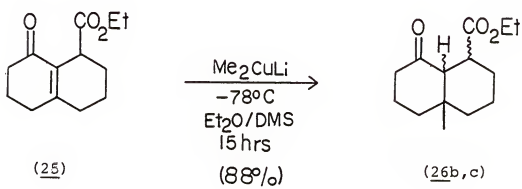
The next step, Swern oxidation ($DMSO/COCl_2$)[35] in methylene chloride, gave 84% combined yield of the octalenones (25) and (25').



(23, 24) (25) (25')

Double bond isomerization to give the unsaturated ketones occurred readily in this oxidation step. The ratio of ketone (25) to (25') was 71:29 for the addition path using dienol (14); however, a reversal of regioselectivity (39:61) was observed for silylether (31) derived oxidation products. Whether this reversal of regioselectivity is due to absence of hydrogen bonding or steric bulk of silyl ether in (31) cannot be ascertained at this time. Nevertheless, synthetically, this result shows promise for regiocontrol in the intermolecular Diels-Alder pathway. The 1,3-adduct (25) was separated from 1,4-adduct (25') (20:80 ether:hexanes on silica gel) without difficulty. The previous Diels-Alder products were not readily separable by either flash column

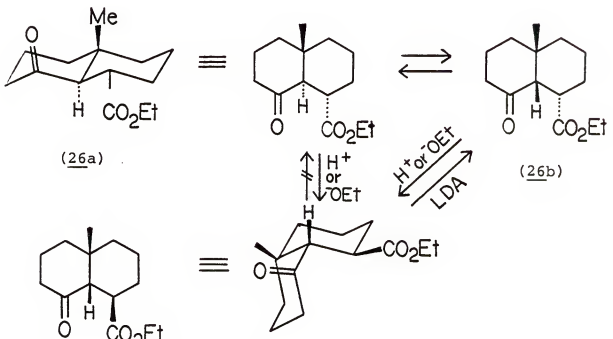
chromatography or preparative G.C. (Carbowax 20). The next step, 1,4-addition of dimethylcopper lithium to ketoester (25) went smoothly to afford an 88% yield of ketoesters (26b,c). The cis-ring juncture was established on the basis of spin-spin coupling constants for the H_8, H_{8a} protons and the demonstration of nuclear overhauser effect (NOE) enhancement for the angular proton (H_{8a}) in 26b.



(25) (26b,c)

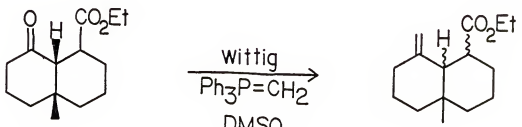
Before attempting the conversion of the ester group of (26b,c) into an isopropenyl group, efforts were made to isomerize the ketoester to give the trans decalin ring juncture, i.e (26a) however, under base catalyzed conditions the attempted equilibrations failed presumably; because of the facile epimerizability of the ester α-proton. Attempted cis/trans

equilibrations catalyzed by p-toluenesulfonic acid were also unsuccessful. Apparently the accessibility of the more stable cis,cis-isomer (26c) under equilibrating conditions preempts the formation of the trans,trans-decalin (26a).



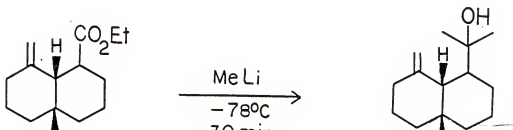
(26a) (26b) (26c)

In the hope that we might be able to bring about the equilibration in a later synthetic step, methylenetriphenylphosphorane was used to convert ketoester (26c) into methylene ester (32).



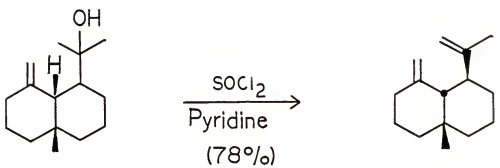
(26c) (32)

Treatement of ester (32) with excess methyllithium resulted in the tertiary alcohol (33).



(32) (33)

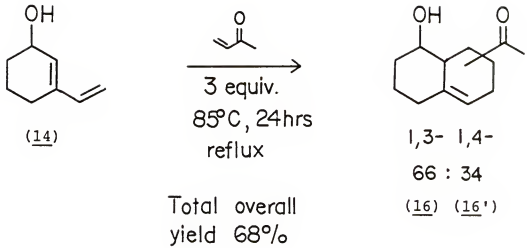
Tertiary alcohol (33), when treated with thionyl chloride, gave 1-methylene-4a-methyl-8-isopropenyldecahydronaphthalene (34). It was determined from spectroscopic data that the ring junction was cis,cis, not trans,trans as required for ß-gorgonene. Therefore, this approach was not pursued further, and instead the approach via the hydroxyketones (16) was investigated.[36,37]



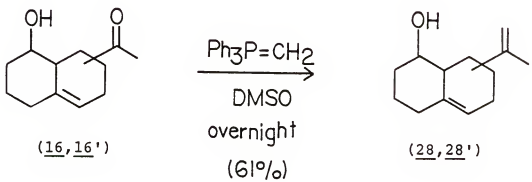
(33) (34)

Methyl vinyl ketone as dienophile

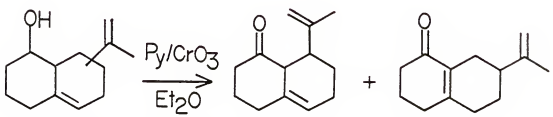
Refluxing vinyl cyclohexenol (14) with excess methyl ketone overnight at 100°C gave 4 major components in the ratio 66:34 for 1,3-adducts (16); 1,4-adducts (16') which were identified by analysis of the products of the oxidation sequence in a later step.



After column chromatography on silica, the crude products were treated with methylenetriphenylphosphorane to convert the methyl ketone into the isopropenyl alcohol (28).



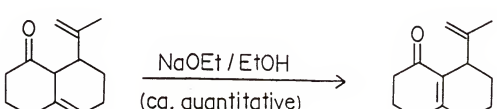
The alcohols (28,28') thus formed were oxidized with pyridine/CrO_3 to produce 2 major compounds, (35) and (36) in a total yield of 53%.



(28,28') (35) (36)

Attempts to use the Swern oxidation procedure in the above resulted in poor yields. Flash chromatography, performed on silica gel with 20:80 ether:pentane, clearly separated the 1,3-adduct (35) from (36).

In basic media (sodium ethoxide/ethanol), unsaturated ketone (35) was converted into the unsaturated ketone (27) in essentially quantitative yield.

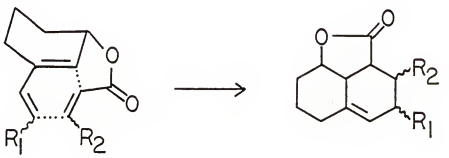


(35) (27)

Conjugate 1,4-addition of this ketone (27) will be discussed later.

Use of Intramolecular Diels-Alder (IMDA) Approach

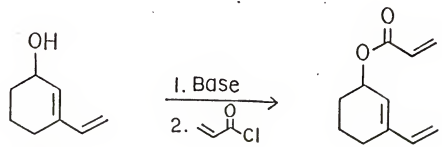
Probably, the most attractive feature of IMDA[38,39] is the opportunity to control the stereochemistry of at least four stereo centers in the products. If we start with a defined geometry for the diene and dienophile, we can derive the stereochemistry of the developing centers, provided the mode of addition (exo-endo) is predictable.



Several experimental procedures for the preparation of ester (18), the substrate for the intramolecular reaction, are summarized in Table 1.

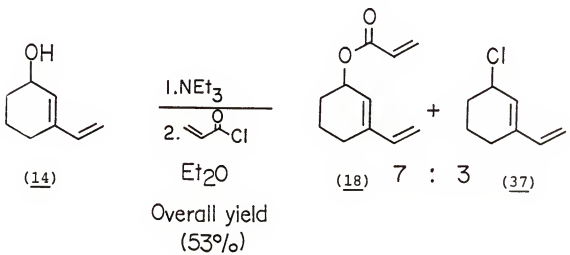
Table 1. Synthesis of 3-vinylcyclohex-2-enyl propenoate (18) under various conditions

Entry	Base	Solvent	Temperature (°C)	Reaction time	Yield(%)
1.	NaH	Et_2O	-78	30 min.	55
2.	NaH	Et_2O	-78	1 hr	43
3.	DMAP	Et_2O	0	1 hr	31
4.	n-BuLi	Et_2O	-78	15 min.	94
5.	n-BuLi	Et_2O	-78	15 min.	88
6.	NEt_3	Et_2O	0	1 hr	48
7.	NEt_3	Et_2O	0	1 hr	42



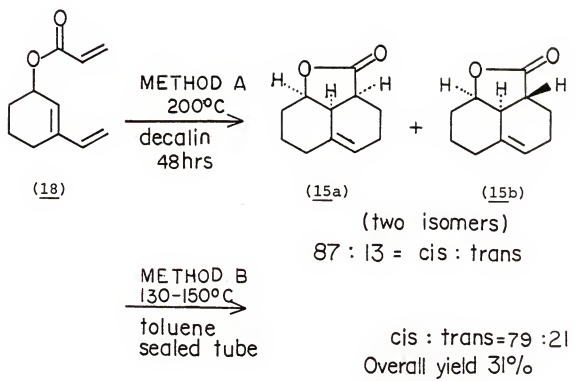
(14) (18)

Deprotonation of alcohol (14) with n-BuLi at -78°C, followed by addition of acryloyl chloride at -30°C for 5 min. gave the best results. Triethylamine was the worst since it always produced side product (37) in a 3:7 ratio with ester (18).



Cyclization was carried out under two different sets of conditions as shown in Scheme 8.

Scheme 8


METHOD A
200°C
decalin
48hrs
(18)
(15a)
(15b)
(two isomers)
87 : 13 = cis : trans
METHOD B
130-150°C
toluene
sealed tube
cis : trans=79 :21
Overall yield 31%

Overall yields were not high. Gas chromatographic analysis showed a 65% yield, but the actual isolated yield after chromatography on silica gel was 28-30%, for Method A. For Method B in which the ester (18) was heated with toluene in a sealed Pyrex tube at 130-150°C for several days, a slightly higher yield (33%) was obtained. Usually heating in decalin at 200°C produced a large amount of polymeric material (Scheme 8).

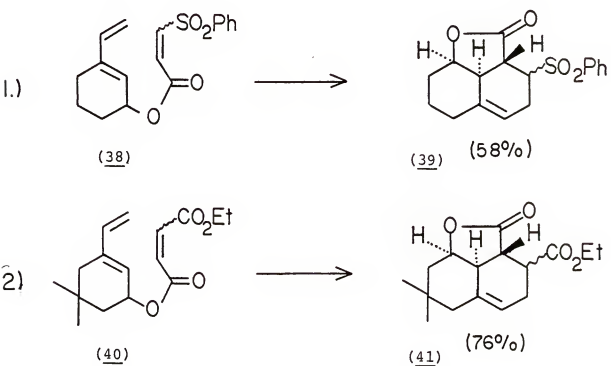
In an earlier investigation[40] using a different diene moiety with more electrophilic internal dienophile units, considerably increased yields were observed for this cyclization.

The stereochemical course of the cycloadditions described herein was elucidated by homonuclear ^{1}H-NMR experiments at 300 MHz (see Experimental) and was that predicted by considering the various transition state interactions. Examinations of molecular models for the intramolecular Diels-Alder substrates revealed that the transition state orientation in which the tether between the diene and dienophilic units is exo is readily accessible. However, the alternative orientation in which the tether is endo with respect to the diene is quite strained. We therefore expected the stereochemistry for the tricyclic adducts, and these expectations were confirmed by high field ^{1}H-NMR spectroscopy.

It should be noted that this synthetic route to the tricyclic adducts conveniently introduces three asymmetric

centers with complete relative stereocontrol, ready for further elaboration. This signals that the ethoxycarbonyl and phenylsulfonyl or ester terminated vinyl fragment are more willing partners in the intramolecular Diels-Alder reaction than the unactivated vinyl ester functional group. The yields of substituted ones are much higher (Scheme 9).

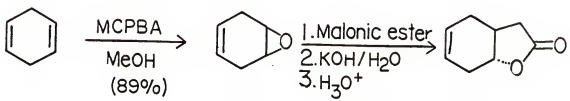
Scheme 9



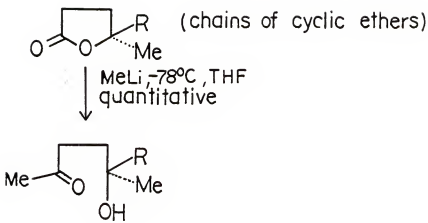
Studies on the Model System, trans-γ-Lactone of 2-Hydroxycyclohex-4-ene Acetic acid (17)

The lactone (17) was derived from cyclohexadiene as shown in Scheme 10.

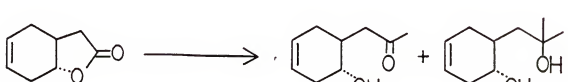
Scheme 10



Epoxidation[41] of cyclohexadiene with m-CPBA went smoothly with 67% overall yield for the 2 steps. The reaction with malonic ester was carried out as described by Vanderwerf and Newman.[42] Opening of the γ-lactone (17) was initially carried out using the procedure of Fukuyama.[43] He reported that addition of methyllithium in THF to γ-butyro lactone shown below at -78°C gave a quantitative yield of ring-opened hydroxy ketone. Application of this method to lactone (17)



resulted in a mixture of methylketone (43) and diol (44) under several sets of reaction conditions. These are listed in Table 2.



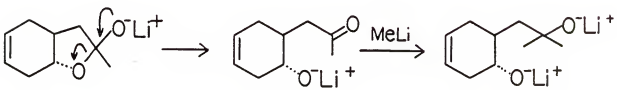
(17) (43) (44)

Table 2. Reaction of trans-lactone of 2-hydroxycyclohex-4-ene acetic acid (17) with methyllithium (MeLi)

Entry	Reagent	Solvent	Temperature (°C)	Reaction time	Products (%)[a]		
					(17)	(43)	(44)
1.	MeLi	Et_2O/THF	-78	2 hrs	4	56	40
2.	MeLi	THF	-84	2 hrs	6	62	32
3.	MeLi	THF	-110	30 min.	76	24	0
4.	MeLi	THF	-110	2 hrs	15	77	8

a. results of G.C. analysis

It was thus possible to minimize the production of unwanted side product (44) by lowering the temperature to -110 °C to prevent a second attack by methyllithium by in effect, freezing out the intermediate (45) (Entry 3, Table 2). However, the reaction was sluggish and difficult to control at this low temperature because of the freezing of the reaction mixture. Therefore, another method was necessary which could quench the intermediates before another nucleophilic attack occurred.

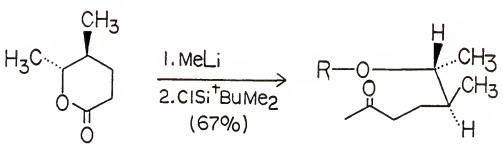


(45) (46) (47)

Recently, the use of organosilicon compounds as reagents and intermediates in organic synthesis has become a field of considerable importance. It can provide strategic pathways which may not be achievable with other reagents. The trimethylsilyl group is well known as a protecting group for amino, hydroxyl and terminal alkynyl groups.[44a]

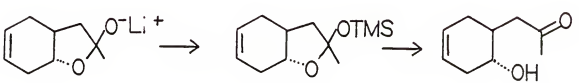
It has also been used for oxygen capture with elimination to form olefins and in the stabilization of α-carbanions and ß-carbanium ions.[44b] However, trimethylsilyl ethers are too susceptible to solvolysis in protic media to be broadly useful in synthesis.[44c] In the case of the opening of the lactones, however, this susceptibility could be advantageous because this group can easily be removed during work up after the silyl group has been used as a scavenger for alkoxide ion liberated during the reaction. Thus the reaction intermediate is kept unreactive toward a possible second attack by the nucleophile. The generation of specific alkoxide anions which coordinate with trimethylsilyl chloride provides a potentially valuable method for opening of the lactone to hydroxyketone.

The synthetic studies of 1,7-dioxaspiro[5.5]undecan-4-ones by Williams (1983)[45] provide an example in which the silyl reagent was used to reduce the problems mentioned above.



Addition of methyllithium (1 eq. THF, -78°C.) and subsequent silyl ether protection ($ClSi^tBuMe_2$, CH_2Cl_2, DMAP) was reported to give methylketone in 67% yield for the 2 steps in his case.

We attempted to quench the intermediate (45) in the reaction of (17) with methyl lithium by in situ TMSCl at very low temperatures.



(45) (48) (43)

This procedure gave more satisfactory results as shown in Table 3.

Table 3. Reaction of lactone (17) with methyllithium in the presence of trimethylsilylchloride (TMSCl)

Entry	MeLi equivalent	TMSCl equivalent	Solvent	Temperature (°C)	Reaction time	Products (%)		
						(17)	(43)	(44)
1.	2	2	THF	-84	2 hrs	5.0	30.0	65.0
2.	2.6	5	THF	-109-RT	3	55.1	38.5	2.5
3.	2.6	10	THF	-109	3	76.6	15.7	0.0
4.	4.6	7	THF	-109	2	67.2	26.3	0.0
5.	6.8	7	THF	-109	2	64.9	19.8	0.0
6.	9.5	7	THF	-109	2	66.9	25.8	0.0
7.	13	7	THF	-109	3	52.5	35.2	0.0
8.	15	7	THF	-109	3	55.4	16.8	0.0
9.	15	7	THF	-109-RT	overnight	0.7	9.0	88.7
10.	2	5	THF	-120--90	3	80.2	17.3	0.0
11.	2.2	5	THF	-120--65	2	57.3	8.4	0.0
12.	4	5	THF	-109--40	3	29.5	45.6	0.0

Percentage of products were based on G.C. analysis.

No diol (44) was produced as long as TMSCl was in excess even when the temperature was gradually increased to room temperature (except in one case, possibly due to a stirring problem). Even below -100°C, TMSCl still competes with lactone (17), and therefore an excess of the reagents was necessary for the reaction to go to completion. Nevertheless, this proved to be a very useful method for limiting the formation of diol (44).

When MeLi was in excess, and the temperature was increased, the diol (44) was a major product as expected.

Flash chromatography with silica could not separate the product (43) from diol (44) efficiently. Isolation of hydroxyketone (43) was attempted with several different columns by preparative gas chromatography. Carbowax 20 (20%) gave the best separation. Tetrahydrofuran was used as a solvent extensively since lactone (17) was not very soluble in diethyl ether at temperatures below -78°C.

The utility of copper complexes (Me_2CuLi, Me_3CuLi_2)[46] was also examined for this conversion as shown in Table 4. These experiments demonstrated that the copper complexes were not useful reagents for our purpose.

Temperatures below -120°C could not in general be used because the reaction mixture freezes. Methyl Grignard reagent[47] was also tried at -78°C but gave diol (44) as the major product.

Table 4. Reactions of lactone (17) with organocopper reagents

Entry	Copper reagents	Equivalent used	Solvent	Temperature °C	Reaction time	Products		
						(17)	(43)	(44)
1.	Me_2CuLi	1.0	Et_2O/DMS	-78-RT	overnight	100.0	0.0	0.0
2.	Me_3CuLi	4.5	Et_2O/DMS	-78	2 hrs	1.5	9.5	85.5
3.	Me_3CuLi	3.6	Et_2O/DMS	-78	20 min.	13.1	10.6	76.3

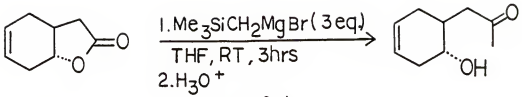
Percentage of the products were based on G.C. analysis

In 1946, Whitmore and Sommer[48] described for the first time, the preparation of trimethylsilylmagnesium chloride (49) from chloromethyltrimethylsilane and magnesium metal.

$$Me_3SiCH_2Cl \xrightarrow{Mg \text{ or } Li} \underset{(49)}{MeSiCH_2MgCl} \text{ or } \underset{(50)}{Li}$$

It was not until 1968 that Petersen[49,50] demonstrated the valuable synthetic uses of this Grignard reagent for the preparation of terminal alkenes. It is also interesting to note that Sommer also described in detail the preparation of trimethylsilylmethyllithium (50), a reagent that quickly found very useful applications. Trimethylsilylmethyllithium (50) was prepared from chloromethyltrimethylsilane and lithium metal in olefin-free pentane.

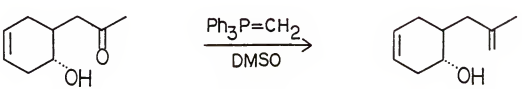
Application of reagent (49) to avoid the problems previously encountered using methyllithium with lactone (17) gave the most promising results heretofore. Thus, 3 equivalents of silyl Grignard reagent $(CH_3)_3SiCH_2MgBr$ (49) in THF reacted with lactone (17) at room temperature for 3 hours to produce hydroxyketone (43) in 73% yield after acidic workup.



(17) (43)

Gas chromatographic analysis of the product showed no traces of diol (44). We also investigated the sensitivity of this reagent toward steric factors by testing with a series of substrates as shown in entries 1-9 (Table 5).

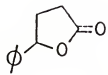
The conversion of ketone (43) to alkene (51) was accomplished using methylenetriphenylphosphorane in DMSO at room temperature in 74% yield.



(43) (51)

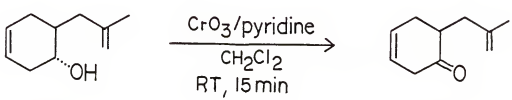
Table 5. Reactions of lactones with trimethylsilylmethyl magnesium chloride (Me_3SiCH_2MgCl) in various conditions

Entry	Substrates	Me_3SiCH_2MgCl equivalent used	Solvent	Temperature	Reaction time	Product & Yield(%)
1.		2.0	Et_2O	RT	3 hrs	 (81%)
2.	"	2.0	THF	RT	Overnight	" (55%)
3.	"	10.0	THF	60	3 hrs	Mess
4.		2.0	Et_2O	RT		 (15%)

5.		2.0	THF	60	6hrs	 (5%)
6.		5.0	Et_2O	RT	Overnight	No reaction
7.		5.0	Et_2O	RT	Overnight	No reaction
8.		5.0	Et_2O	RT	Overnight	No reaction
9.		5.0	Et_2O	RT	Overnight	No reaction

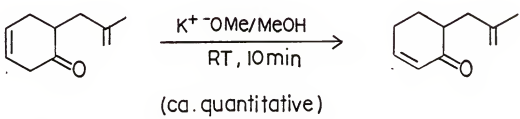
Analytical G.C. showed the same retention time (methylsilicon-crosslinked capillary column) for the hydroxyketone (43) and the olefin product (51), but TLC gave different R_f values. At this stage, the diol (44) which was present as an impurity in hydroxyketone (43) was easily removed by flash chromatography (Silica 200-400 mesh). The product (51) eluted with 20:80 ether:pentane and the diol (44) with 60:40 ether:pentane. In the original workup alcohol (51) was extracted with ether since the usual solvent (pentane) was not sufficiently polar. Methylene chloride proved to be too polar and extracted DMSO. After extraction with ether, unreacted phosphonium salts were removed by chromatography on silica to give the pure product (51).

Oxidation[51] of hydroxyolefin (51) with a basic oxidizing reagent such as chromium trixoide/pyridine complex in methylene chloride resulted in 62% yield of (52) after purification.



(51) (62%) (52)

Isomerization of the unsaturated ketone (52) was carried out in basic methanol solution to give the α,β-unsaturated ketone (53) in quantitative yield.

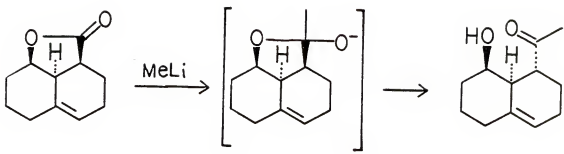


(52) (53)

Attempts to isomerize this ketone (52) under acidic conditions (50% H_2SO_4) were unsuccessful in a previous reaction.

Opening of Lactone (15) via Monomethylation

Synthetic methods to obtain hydorxyketone (16b) from lactone (15a) have been extensively studied with MeLi, MeLi and TMSCl, trimethylsilylmethyl Grignard reagent and a cyclic titanium complex precursor to Tebbe's titanoscenylmethylene reagent.[52]

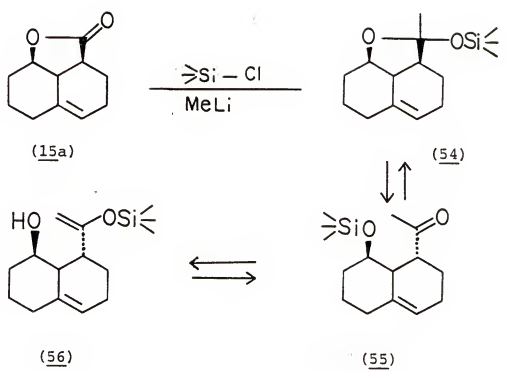


(15a) (16b)

The major problem encountered here was that once the intermediate was formed, a second attack by the organometallic reagent occurred since the open ketone is more reactive than lactone (15a).

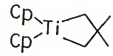
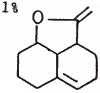
As previously discussed in this Chapter, an attempt was made to quench this intermediate with TMSCl as shown in Scheme 11.

Scheme II

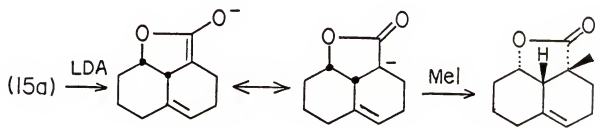


Many of the conditions which proved useful in our model lactone system (17) were unsatisfactory when applied to tricyclic molecule (15a). This lactone with cis-cis, cis-cis stereochemistry at C-8a and C-8b, C-8b and C-2a was unexpectedly unreactive towards strongly basic nucleophiles. One reason is apparently that the acidic α-proton at C-2a is stereoelectronically in an ideal position for abstraction by the base. Thus the lactone ring may exist as the enolate anion which protects it from nucleophilic attack under basic

Table 6. Opening of lactone (15) by various reagents

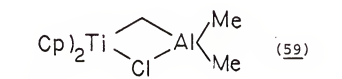
Entry	Reagents	Solvent	Reaction time	Temperature °C	Products & Yield(%)
1.	TMSCl/MeLi	THF	2 hrs	-100	No Reaction
2.	Me_3SiCH_2MgCl	Et_2O	2 hrs	RT	No Reaction
3.	Tebbe	Et_2O	2 hrs	RT	5%
4.		Benzene	15 min.	RT	91%  (57)
5.	Me_3SiCH_2Cl/ n-BuLi	Et_2O	3 hrs	-78	Complex mixture
6.	$Me_3SiCH_2Se\emptyset$/ n-BuLi	Et_2O	3 hrs	-78	Complex mixture

conditions at low temperature. This enolate anion was generated in a separate experiment by treatment with LDA. Methylation of this anion with methyl iodide gave a single stereoisomer (58), the product of kinetically preferred pseudoaxial attack on the enolate ion.

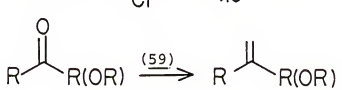


(58)

The titanium alkylidene (59), Tebbe's reagent,[53] has been reported as a methylenation agent for the conversion of ketones to olefins and esters to vinyl ethers.

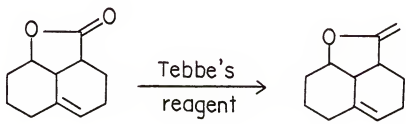


(59)



It was found[53] that the crude reaction mixture formed by the combination of titanocene dichloride and 2 equivalents of $AlMe_3$ could be used directly to effect methylene transfer.

Optimization of the reaction conditions was performed by the procedure of Cannizzaro and Grubbs[54] (1985).

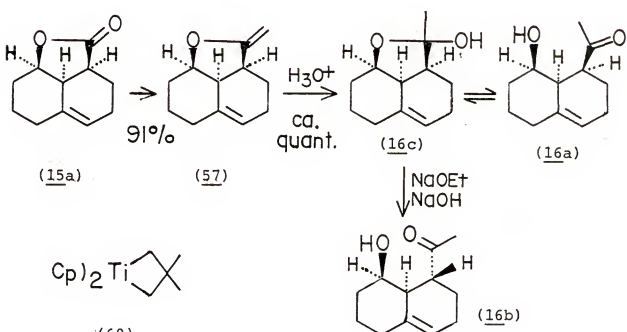


(15a) (57)

Surprisingly, the yield was very low with less than 5% in our case. This low yield might be caused either by low reactivity of the lactone (15a) or failure to prepare Tebbe's reagent correctly. Repeat reactions failed to improve the results.

In 1985, Grubbs and Straus[55] introduced the titanocyclobutane (60), a related methylenation reagent,[56] which does not have the problem of associated alkyl aluminum contaminants.

This reagent served as an excellent methylenating agent, giving a 91% conversion of lactone (15a) to tricyclic enol ether (57). After quenching the reaction mixture with acid, NMR and IR spectral analysis confirmed that vinyl ether (57) had been hydrolysed to the cyclic hemiketal (16c)/hydroxyketone (16a). Treatment of this methyl ketone with ethanolic sodium ethoxide resulted in epimerization to trans-hydroxyketone (16b) for which all spectroscopic data matched exactly with one of the intermolecular Diels-Alder adducts of (14) with methyl vinyl ketone.

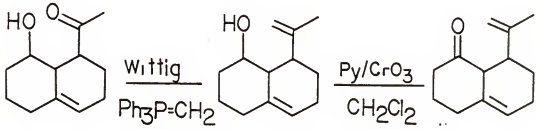


(15a) (57) (16c) (16a)

(60) (16b)

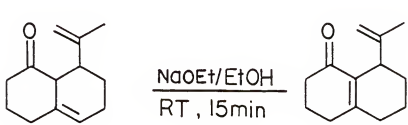
Synthetic Route to α,β-Unsaturated Ketone (27) from the Hydroxyketone (16b)

The Wittig reaction of hydroxyketone (16b) gave a 73% yield of hydroxydiene (28). Duplicate reactions were carried out at room temperature with yields varying from 55% to 73%. Oxidation of alcohol (28) with pyridine/CrO_3 agent gave (35) as the major product in 60% yield.



(16b) (28) (35)

α,β-Unsaturated decalone (27) was then prepared by isomerization of unsaturated decalone (35) with ethanolic sodium ethoxide at room temperature. Methanolic sodium methoxide acted similarly giving approximately quantitative yield.



(35) (27)

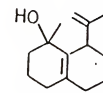
Conjugate 1,4-Addition to the Sterically Hindered α,β-Unsaturated Decalone System (27)

The reactions of several different organocopper reagents with α,β-unsaturated decalone systems have been investigated. The chemical behavior of the various organocopper compounds varied greatly and was significantly affected by the solvent employed. It was often necessary, therefore, to examine empirically several organocopper species and to use different solvents and temperatures to arrive at optimum choice of reagent and conditions for the desired transformation.

In our experiments, catalytic organocopper compounds were more reactive when prepared from Grignard rather than organolithium reagents. Pure stoichiometric organocopper compounds (RCu)[57] are known to be less reactive than the corresponding cuprate species. We also used heterocuprate species such as MeCuCNLi, $Me_2CuCNLi_2$.[58] Organocopper-borane[59] complexes reacted in a very similar manner to the reagents prepared from Grignard reagents.

In our system, 1,4-addition of organocopper reagents was successful when the ester functional group was located at C-8 of the octalenone. When, however, the ester group was changed into an isopropenyl group, conjugate 1,4-addition could not be detected despite numerous attempts. When the reactivity of the copper reagent was increased, only 1,2-addition was observed on octalenone system (27). This might be due to steric or electronic effects of the isopropenyl group, but the reason is not clear at present. The results of our experiments are shown in Table 7.

Table 7. 1,4-Addition trials on α,β-unsaturated decalin system (27) with homo-organocopper reagents

Entry	Reagents	Equivalent used	Solvent	Temperature °C	Reaction time	Results
1.	Me_2CuLi	2	Et_2O	-78-RT	Overnight	No reaction
2.	Me_2CuLi	2	THF	-78-RT	Overnight	No reaction
3.	Me_2CuLi	2	Et_2O/DMS	-78-RT	Overnight	No reaction
4.	Me_3CuLi_2	1	Et_2O	-78	5 hrs	No reaction
5.	Me_3CuLi_2	2	Et_2O	-78-RT	Overnight	 (42%) (61)
6.	Me_5CuLi_3	2	Et_2O/DMS	-78-RT	Overnight	"

Several recent reports have been concerned with unusual reactivity of reagents prepared by mixing lithium dialkyl- or diarylcuprates with the corresponding organolithium compounds.[59-62] For example, the reagent having the stoichiometry $LiCuPh_2.PhLi$ appears to be more reactive than $LiCuPh_2$ in metal-halogen exchange reactions and coupling with aryl bromides. Also it has been recently found that a 3:2 mixture of $LiCuMe_2$ and CH_3Li is more stereoselective toward 4-tert-butylcyclohexanone than either Me_2CuLi or CH_3Li. In addition, mixtures of Me_2CuLi and CH_3Li have been found to react with diaryl ketones as a reducing agent more powerfully than either Me_2CuLi or MeLi. These reports suggest that lithium compounds are capable of reacting to form complexes of the type Me_3CuLi_2 and Me_4CuLi_3.

Hence, we decided to examine the reactions of higher order cuprates with enones so as to compare and contrast them with lower order cuprates, Me_2CuLi. These experiments with higher order cuprates resulted in 1,2- addition to our system (27). (Entry 5,6, Table 7).

Ashby's study[63] of the higher order species confirmed that Me_3CuLi_2 exists to an appreciable degree in equilibrium with Me_2CuLi and free MeLi. This complex (i.e., $Me_2CuLi.MeLi$) is known to react extremely rapidly with ketones. In many cases it delivers CH_3^- in a 1,2- sense when reacted with enones. Hence the key question remained as to whether our enone (27) would be sufficiently reactive toward higher organocuprates so as to compete with any free RLi which would be expected

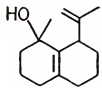
to add in a 1,2-fashion. Whitesides (1974)[64] pointed out that the reactivity of organometallic groups in mixed cuprates is qualitatively intermediate between the reactivity of the constituent components. That is, a diorganohomocuprate is expected to be considerably more reactive than the corresponding mixed cuprate containing one transferable group and one residual ligand.

By combining the merits of both CuCN based and higher order reagents, it was anticipated that a reactive hybrid species should result from the combination of two equivalents of RLi and one equivalent CuCN. It was this hypothesis which prompted the investigation into the nature, synthetic potential, and scope of the higher order, mixed organo cuprate reagent,[65] $Me_2CuCNLi_2$. (Entry 3,4, Table 8)

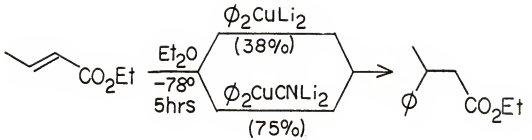
$$2\ MeLi + CuCN \rightarrow Me_2CuCNLi_2$$

Differences in reactivity between Gilman reagents, (R_2CuLi), and $R_2CuCNLi_2$ have been compared, for example, in reactions of Ph_2CuLi and $Ph_2CuCNLi_2$. To each of these cuprates, under identical conditions, was added equal quantities of ethyl crotonate. The higher order reagent afforded ca. twice the yield of conjugate adduct.

Table 8. 1,4-Addition trials on α,β-unsaturated decalin system (27) with heteroorganocopper reagents

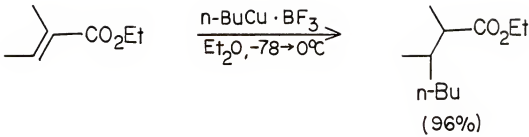
Entry	Reagents	Equivalent used	Solvent	Temperature °C	Reaction time	Results
1.	MeMgBr/ CuBr.DMS(10%)	2	Et_2O	-78-RT	Overnight	 (61) (82%)
2.	$Me_5Cu_3(MgBr)_2$	2	Et_2O	-78-0	6 hrs	" (74%)
3.	$Me_2Cu(CN)Li_2$	2	Et_2O	-78-0	5 hrs	" (90%)
4.	$Me_2Cu(CN)Li_2$	2	Et_2O	-78-RT	Overnight	" (64%)

5.	$MeCu.BF_3$ (CuBr.DMS)	2	Et_2O	-78-RT	5 hrs		(62) (48%)
6.	$MeCu.BF_3$ (CuI)	2	Et_2O	-78-RT	Overnight		(62) (55%)

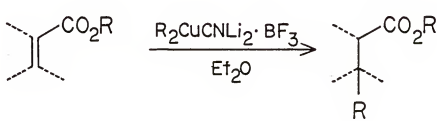


While $R_2CuCNLi_2$ conjugate addition perform well on β-monosubstituted enoate esters. It was discovered that increasing substitution about the olefin resulted not only in decreasing yields, but substantial numbers of undesired side products. Thus, α,β- and β,β-disubstituted esters led to disappointing results, principally due to contamination arising from a 1,2-addition/1,4-addition sequence. For example, the ethyl ester of tiglic acid, when treated with n-$Bu_2CuCNLi_2$, afforded only dialkylated ketone.

The conjugate addition of conventional diorganocuprates to α,β-unsaturated esters has met with only limited success owing to competitive reaction at the carbonyl center in some cases. Recently, Yamamoto[66] described the Lewis acid activated organocopper reagent (n-BuCu.BF_3) which represents a valuable alternative to n-Bu_2CuLi for inducing 1,4-addition to enoates. The conjugate addition of higher order cyanocuprates has also been evaluated in this context and the



results of this study have recently appeared. Insofar as β-unsubstituted examples are concerned, short reaction times, low temperatures, and only a slight excess of reagent again highlight their appeal.



Thus, while cyanocuprates appear to be the reagents of choice for enoates bearing solely β-substituents, the Yamamoto reagent is superior for the reactions of more highly branched adducts. Application of $MeCu.BF_3$ to octalenone (27)

(Entry 5 and 6, Table 8) resulted in apparent 1,2-addition followed by dehydration on work up. There was no evidence for conjugate 1,4-addition of a methyl group even with this Lewis acid catalyzed copper reagent. Although 1,4-addition of organocopper reagents is known to be slow, when the unsaturated system is tetrasubstituted, the contrast between the results of Boeckman and our results, indicates that additional steric hindrance from the isopropylidene group is sufficient to prevent 1,4-addition. This extra steric hindrance is as yet undocumented and is worthy of further investigation. Other attempted conversions of the ketone (27) to potentially useful synthetic intermediates are shown in Table 9. In the case of the C-8 ester-substituted octalenone (23), the classical dimethylcopper lithium gave the 1,4-adduct without difficulty in contrast to the results discussed above.

Table 9. Conversions of α,β-unsaturated decalin system (27) with various reagents

Entry	Reagents	Solvent	Temperature °C	Reaction time	Products & Yields(%)
1.	$CH_2=\overset{+}{S}(O)Me_2I^-$	DMSO	RT	Overnight	No reaction
2.	$H_2O_2/^-OH$	H_2O	0	5 hrs	 46% (63)
3.	Ethylene diglycol	Benzene	reflux	48 hrs	 12% (64)
4.	Dibal-H	Et_2O	-78	2 hrs	 95% (65)

CHAPTER IV
EXPERIMENTAL

General

Melting points were recorded using a Thomas-Hoover capillary melting point apparatus. Analyses were performed by Atlantic Microlab, Inc. of Atlanta, Georgia.

Spectra

Infrared spectra were recorded on either of two instruments: a Perkin-Elmer 137B or a Perkin-Elmer 283B Spectrophotometer. KBr pellets were made of the solids, and the liquids were run neat. Routine mass spectra were obtained on an Associated Electronics Industries (AEI) model MS-30 mass spectrometer at 70 eV. High resolution mass determinations were handled on the same instrument further equipped with a Nova Systems 4 Computer. Proton NMR spectra were run on either a Varian Model A-60, 60 MHz spectrometer or a Varian Model EM-360, 300 MHz, 60 MHz instruments. Chemical shifts were recorded relative to tetramethylsilane (TMS) at 0.00. ^{13}C NMR spectra were recorded on a JEOL model FX-100 instrument with chemical shifts relative to the deuterochloroform resonance at 77.00.

Reagents and Solvents

The solid reagents were checked for purity by melting point and many were purified by recyrstallization or drying prior to use. The alkyllithium solutions were titrated using 2,5-dimethoxybenzylalcohol. Some of the liquid reagents were purified by distillation. Solvents such as tetrahydrofuran (THF) and diethyl ether were distilled from sodium-benzophenone. Dimethyl sulfoxide (DMSO) and methylene chloride were distilled from calcium hydride (CaH_2) and stored over molecular sieves.

Apparatus and Technique

All the reactions were run in glassware that was filled with an inert atmosphere of nitrogen or argon. Liquid reagents were introduced into the reaction vessel via standard syringe techniques. Flash chromatography and preparative gas chromatography were used for the isolation of pure materials.

Preparation of 3-vinylcyclohexe-2-enol (14). 3-Vinylcyclohex-2-enone (30) (25.7g, 0.184 mol) was placed in a 1000 ml 3 necked round bottom flask with 300 ml of Et_2O. While the mixture was stirred with a mechanical stirrer at 0°C, Dibal-H (1.0 M sol. in hexane, 368 ml, 0.368 mol) was introduced via 2-way needle slowly for an hour period. The reaction mixture was stirred at 0° C for an additional hour, and the temperature was allowed to increase to room temperature and stirring was continued for an additional four hours. The reaction mixture was filtered through glass wool quickly

and quenched with 5% HCl solution, extracted with 3 x 500 ml of Et_2O and washed with $NaHCO_3$ solution, brine and dried over Na_2SO_4. The solvent was evaporated with a rotary evaporator under reduced pressure, and the crude product distilled with Kugelrohr apparatus to give a colorless oil as the product. Yield, 92%: NMR($CDCl_3$) δ 1.73, 2.12 (m, 7H), 4.40 (m, 1H), 5.30 (m, 2H), 5.90 (bs, 1H), 6.45 (m, 1H); IR (neat) 3380, 2915, 1675, 1455, 1358, 1195, 1090; MS, m/e 124, 106, 97, 83, 69, 55, 41.

Preparation of 2a, 3,4,6,7,8,8a,8b-octahydro-2H-naphtho-(1, 8-bc)furan-2-one (15). Vinyl ester (18) was placed in a 100 ml round bottom flask with 45 ml of freshly distilled decalin under N_2. The mixture was heated to 190°C and refluxed overnight. G.C. analysis showed 22% of starting material was still present. The reaction vessel was heated again at 205°C for an additional 24 hours. After cooling to room temperature, the reaction mixture was chromatographed on 30g of silica with hexane to remove decalin. The product was recovered with 30/70 ether/pentane fractions. After evaporation of solvent, the crude product was a light yellowish oil. G.C. analysis showed two isomers (15a) and (15b) in the ratio 75:25. Isolated total yields after chromatography, 30%: (15a) NMR($CDCl_3$)δ300 MHz, 1.1-2.3 (m, 10H) 2.83 (m, 1H), 2.92 (m, 1H), 4.56 (m, 1H), 5.60 (s, 1H); MS, m/3 178, 150, 132, 117, 104, 91, 79, 65, 51, 39, 28. High resolution MS calcd. for $C_{11}H_{14}O_2$ 178.09983, Found 178.0997.

Preparation of 1-hydroxy-8-acetyl-1,2,3,4,6,7,8,8a-octahydronaphthalene (16b). In a 50 ml round bottom flask, 20 ml of absolute ethanol was placed under N_2. Sodium (1.0g, 0.043 mol) was added and the reaction mixture was stirred until the hydrogen evolution ceased. The hemiketal (16c) was injected via syringe with 5 ml of ethanol at room temperature and stirred for 30 min. The reaction mixture was quenched with 30 ml of water and about 15 ml of ethanol was evaporated under reduced pressure. The crude product was extracted with 3 x 100 ml of Et_2O, washed with saturated $NaHCO_3$ solution, brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on a 10 cm short silica column (15g of silica) to give a colorless oil as the product (16b). G.C. analysis showed only one isomer. The yield was quantitative: NMR($CDCl_3$) δ 1.75 (m, 7H), 2.08 (m, 4H), 2.21 (s, 3H), 2.55 (m, 1H), 2.95 (m, 1H), 3.75 (m, 1H), 5.78 (b.s. 1H); IR (neat, 3450, 2960, 1695, 1430, 1345, 1160, 1075; ^{13}C NMR, 212.0, 135.3, 122.7, 68.6, 49.4, 42.6, 34.5, 33.0, 29.0, 25.5, 24.6, 20.3.

Preparation of 1-hydroxy-8-acetyl-1,2,3,4,5,6,7,8,8a-octahydronaphthalene (16b) via intermolecular Diels-Alder reaction. 3-Vinylcyclohex-2-enol (14) (0.500g, 0.00463 mol) was placed with 3 equivalents of methylvinyl ketone (0.847g, 1.0 ml, 0.0121 mol) in a 10 ml round bottom flask under nitrogen. The reaction mixture was refluxed for 24 hours at 85°C (bath temperature). The reaction vessel was

cooled to room temperature and the excess methylvinyl ketone was removed under reduced pressure. The residue was chromatographed on silica thin layer preparative plate with 20:80 ethyl acetate:pentane to produce a mixture of 1,3-adducts (16b) and 1,4-adducts (16') with the ratio of 66:34. Total overall yield, 0.63g, 79%. Spectroscopic data for (16b) were identical to those given above.

Preparation of 2-methyl-2-hydroxy-2a,3,4,6,7,8,8a,8b-octahydro-2H-naphtho(1,8-bc)furan (16c). In a 50 ml round bottom flask, 100 mg of vinyl ether (57) (0.0005 mol) was placed, and 10 ml of 3N-HCl was added at one portion. The reaction mixture was stirred at room temperature for 10 min. Additional 10 ml of water was then added and extracted with 3 x 100 ml of ether, washed with $NaHCO_3$ solution, brine, water, and dried over $MgSO_4$. After filtration on celite the solvent was evaporated under reduced pressure and the residue was chromatographed on a short silica column (10g) to produce a light yellowish oil after evaporation of the solvent. The yield was quantitative: NMR($CDCl_3$) δ 1.40, 1.72, 2.16, 2.85 (m, 13H), 4.20 (m, 1H), 5.60 (b.s. 1H); IR (neat), 3430, 2900, 1725, 1450, 1440, 1360, 1300, 1175, 1100, 1070, 1020, 990, 948, 962, 875. MS, m/e 192, 177, 149, 121, 99, 87, 80, 72, 65, 59, 45, 37, 28.

Preparation of trans-lactone of 2-hydroxycyclohex-4-ene acetic acid (17). In a 1000 ml round bottom flask, sodium (5.46g, 0.237 mol) was dissolved in 300 ml of absolute ethanol under N_2. The reaction vessel was heated to dissolve sodium and then cooled to room temperature. Malonic ester (27.0g, 0.231 mol) in 50 ml of absolute ethanol was added via syringe over a 5 min. period. After stirring an additional 10 min. at room temperature, cyclohexene epoxide (41) (0.150 mol, 14.1g) was added under N_2. The reaction mixture was warmed to 85°C (bath temperature) and stirred for 5 hours before quenching with 100 ml of water. Potassium hydroxide (20g) was added and the resulting solution heated, with stirring, as alcohol was removed by distillation. After 300 ml of distillate had been collected, an equivalent volume of H_2O was added and the process repeated. After cooling, the solution was acidified with 40 ml of H_2SO_4, and the product was extracted with 3 x 150 ml of CH_2Cl_2. After work-up and evaporation of solvent in vacuo, the residue was distilled to give a white waxy solid; crude yield 28.9g, 82% yield. Recrystallization from hexane gave 19.3g of pure compound; yield 82%: NMR($CDCl_3$) δ 2.35 (m, 7H), 4.25 (m, 1H), 5.75 (m, 2H); IR (neat), 2965, 1770, 1195, 1125, 1020, 920, 854: MS, m/e 138, 91, 84, 79, 66, 54, 44, 29. High resolution MS calcd. for $C_8H_{10}O_2$ 138.0681, Found 138.0670; Anal. calcd.; C, 69.54, H, 7.30, Found C, 69.53, H, 7.30.

Preparation of 3-vinylcyclohex-2-enyl propenoate (18) with sodium hydride as base. In a 250 ml 3 necked round bottom flask, sodium hydride (80% emulsion, 0.871g, 0.0290 mol) was placed under N_2. Dry pentane 2 x 10 ml was added, the resultant slurry decanted and the residue washed twice more with pentane. After removing pentane, 50 ml of Et_2O was added and the temperature was lowered to -78°C with dry ice bath. Vinylcyclohexenol (14) (3.596g, 0.0290 mol, 1 eq.) in 5 ml of ether was injected by syringe for 5 min. period. Acrylic chloride (2.370g, 1 eq.) was then added slowly dropwise over a 10 min. period and the reaction mixture was stirred for an additional 30 min. The temperature was allowed to increase to 0°C slowly. The reaction mixture was quenched with NH_4Cl/NH_4OH solution, washed with brine, water and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica with 10/90 ether/pentane solution to give a colorless oil as the product. G.C. analysis showed one clean product; 2.34g, 55% yield: NMR($CDCl_3$) δ 1.83 (m, 4H), 2.20 (m, 2H), 5.91 (m, 8H); IR (neat), 2940, 1720, 1608, 1402, 1292, 1218, 1196, 1165, 1040, 982, 915, 810; MS m/e 178, 123, 106, 91, 78, 72, 65, 55, 44, 40, 32, 28.

Preparation of 3-vinylcyclohex-2-enyl propenoate (18) with n-butyllithium as base. Vinylcyclohexenol (14) (0.100g, 0.000806 mol) was placed in a 25 ml round bottom flask with 5 ml of dry diethyl ether. The reaction vessel was cooled

to -78°C. Butyllithium (0.387 ml, 0.000967 mol, 1.2 eq.) was added via syringe slowly over a 5 min. period and stirred for an additional 10 min. The reaction vessel was warmed to -30° C for 10 min. Then warmed to 0°C and quenched with water. The product was extracted with 3 x 50 ml of diethyl ether and washed with saturated $NaHCO_3$ solution, brine, water and dried over $MgSO_4$. After evaporation of the solvent, the crude product was chromatographed on a short silica column (5 cm, 200-400 mesh, 3g) to produce a colorless viscous oil (18); yield: 0.134g, 94%: spectroscopic data are the same as in the preparation of (18) with sodium hydride as a base.

Preparation of 8-isopropenyl-1,2,3,4,5,6,7,8-octahydronaphthalen-1-one (27). Bicyclic unsaturated ketone (35) (0.50g, 0.00263 M) was dried by azeotropic evaporation with benzene twice and diluted with 3 ml of dry ethanol. In a 25 ml round bottom flask, sodium (0.060g, 1 eq.) was added to 10 ml of ethanol. The reaction mixture was stirred for 20 min. until all hydrogen evolution ceased and the reaction vessel was cooled to room temperature. The previously prepared ketone (49) was then added in one portion and the solution stirred for 15 min. The reaction mixture was quenched with water, and ethanol evaporated under reduced pressure. The product was extracted with 3 x 100 ml of ether and washed with brine, water and dried over $MgSO_4$. After the solvent evaporation, the residue was chromatographed on

silica gel with 20/80 ether/pentane to give a colorless oil as the product (27). The yield was quantitative, 0.49g: NMR($CDCl_3$) δ 1.59 (m, 4H), 1.80 (s, 3H), 2.25 (m, 8H), 3.22 (b.s. 1H), 4.35 (s, 1H), 4.77 (s, 1H); IR (neat), 29.5, 1650, 1450, 1430, 1380, 1310, 1290, 880. MS, m/e 190, 162, 148, 120, 112, 98, 84, 71, 59, 48, 33, 28. High resolution MS calcd. for $C_{13}H_{18}O$ 190.1357, Found 190.1351.

Preparation of 8-carbethoxy-1,2,3,4,6,7,9,8a-octahydronaphthalen-1-ol (23). In a 10 ml round bottom flask, 0.57g (0.0046 mol) of vinyl alcohol (14) was placed with 3 eq. of acrylic ester (1.39g, 1.5 ml, 0.0139 mol) under N_2. Hydroquinone (20 mg) was added to prevent radical polymerization. The reaction vessel was heated at 80°C for 24 hours while stirring, and the temperature was increased up to 100°C and maintained an additional 24 hours. The excess acryclic ester was evaporated under vacuo, and the residue was chromatographed on a silica gel column with 20/80 ether/pentane. After evaporation of solvent the residue was chromatographed again with 10/90 ether/pentane. The products were colorless. G.C. analysis showed 4 major peaks for ester (23), its isomer (24), and the tricyclic lactone (15a). The ratio was (23):(24):(15a)=63:32:5. The products, (23),(24) were used for the oxidation of alcohol without further separation. Total yield: 0.79g, 84%: (23) NMR($CDCl_3$) δ 1.21 (t, 3H), 1.90 (m, 13H), 3.4-4.0 (mb, 1H), 4.10 (q, 2H), 5.58 (b.s., 1H): IR (neat), 3450, 2915, 1728, 1445, 1328, 1300, 1165, 1050; MS, m/e 206, 150, 122, 104, 91, 79, 67, 55, 41; (24)

NMR($CDCl_3$) δ 1.21 (t, 3H), 2.10 (m, 13H), 3.23 (m, 1H), 4.18 (q, 2H), 5.53 (b.s. 1H); IR (neat), 3460, 2919, 1720, 1440, 1375, 1300, 1170, 1050; MS, m/e 206, 133, 104, 91, 79, 67, 55, 41. (15a) NMR($CDCl_3$) δ 1.70-2.50 (m, 10H), 2.90 (m, 2H), 4.64 (m, 1H), 5.67 (s, 1H); MS, m/e 178, 133, 104, 91, 79, 65, 51, 44, 39, 27.

Preparation of 7-carbethoxy-1,2,3,4,6,7,8,8a-octahydronaphthalen-1-ol (24) from 1-(t-butyldimethylsiloxy)-8-carbethoxy-1,2,3,4,6,7,8,8a-octahydronaphthalene. In a 5 ml round bottom flask, siloxyvinyl cyclohexene (31) (0.087g, 0.00037 mol) was placed with acrylic ester (1 ml, 0.0139 mol) under N_2 and 3 mg of hydroquinone was added. The reaction vessel was heated in an oil bath for 5 hours at 80°C, and the temperature was increased to 100°C and stirred overnight. It was cooled down to room temperature, and the excess acrylic ester was evaporated under reduced pressure. The residue was chromatographed on a short silica column to remove polymers. After evaporation of solvent, the products were disilylated with $HOAC/H_2O$ = 1.3 at room temperature for 24 hours. G.C. analysis showed 31% of 1,3-adduct (23), 48% of 1,4-adduct (24) and 21% of unidentifiable materials. Overall yield, 0.051g, 67%. Spectroscopic data are the same as in the preparation of (23) above.

Preparation of 8-carbethoxy-1,2,3,4,5,6,7,8-octahydronaphthalen-1-one (25). A solution of CH_2Cl_2 (10 ml) and oxalyl chloride (0.227 ml, 2.6 mmol) was placed in a 25 ml 3 necked round bottom flask equipped with a magnetic stirrer, a thermometer, and two dropping funnels containing DMSO (0.37 ml, 5.2 mmol) dissolved in 5 ml of CH_2Cl_2 and the hydroxyester (mixture of (23) and (24), 525 mg, 2.34 mmol), respectively. The DMSO was added to the stirred oxalyl chloride solution at -50 to -60°C. The reaction mixture was stirred for 2 min., and the hydroxyester added in 5 min; stirring was continued for an additional 15 min. Triethylamine (4.60g, 6.34 ml, 11.82 mol), was added and the reaction mixture was stirred for 5 min. The system was then allowed to warm to room temperature, 10 ml of water was then added and extracted with 3 x 100 ml of CH_2Cl_2. The organic layer was combined, 4N-HCl was added. It was stirred vigorously for 10 min. with stirring bar, and the crude products were extracted with 3 x 100 ml of Et_2O. This organic layer was washed with saturated $NaHCO_3$ solution, brine, water and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel (30g) in hexane elution with 5%, then 10%, EtOAC to give 225 mg of ketoester (25), 100 mg of (25') with overall yield, 84%: (25) NMR δ 1.22 (t, 3H), 1.81 (m, 5H), 2.30 (m, 7H), 3.48 (b.s., 1H), 4.13 (q, 2H); IR (neat), 2930, 1730, 1663, 1601, 1583, 1360, 1260, 1180; MS, m/e (relative intensity) 222, 176, 149, 131, 120, 105, 91, 77, 65, 55, 39, 29; ^{13}C NMR, 197.2, 174.1,

158.4, 130.1, 59.8, 38.3, 36.9, 30.8, 25.7, 21.5, 18.9, 13.6. (25') NMR($CDCl_3$) δ 1.30 (t, 3H), 2.25 (m, 13H), 4.29 (q, 2H); MS m/e 222, 176, 149, 131, 120, 105, 91, 77, 55, 41, 28.

Preparation of 4a-methyl-8-carbethoxy-1,2,3,4,5,6,7,8,8a-decahydronaphthalen-1-one (26b). CuBr.DMS (4.31g, 0.021 mol) was weighed in a dry box and placed in a 250 ml round bottom flask under N_2. 22 ml of dimethyl sulfide and 22 ml of Et_2O was added. The reaction vessel was cooled down to -30°C and methyllithium (1.5 M, 26.6 ml, 0.40 mol) was injected slowly until all yellow ppt. disappeared, and the solution became colorless. The temperature was increased to 0°C, and ketoester (25) (2.352g, 0.0105 mol) added in 20 ml of ether dropwise at 0°C via syringe. After stirring 4 hours at 0°C, the reaction mixture was quenched with NH_4Cl/NH_4OH solution, extracted with 3 x 150 ml of ether, washed with brine, water and dried over $MgSO_4$. After evaporation of solvent, the residue was chromatographed on silica (20g) with 10/90 EtOAC and hexane mixture to give a colorless oil as the product (26b) and (26c) with ratio of 86:14. The duplicated reaction had only one product (26b). (26b) NMR($CDCl_3$), 300 MHz δ 0.98 (s, 3H), 1.21 (m, 5H), 1.70 (m, 4H), 1.92 (m, 4H), 2.25 (m, 2H), 2.58 (m, 1H), 2.90 (m, 1H), 4.08 (q, 2H); IR (neat), 2940, 1720, 1460, 1175, 1160, 1030, 850. (26c) NMR($CDCl_3$) δ 1.05 (s, 3H), 1.25 (t, 3H), 1.54 (m, 8H), 2.00 (m, 3H), 2.35 (d, 2H), 3.05 (m, 1H), 4.20 (q, 2H); IR (neat), 2940, 1730, 1665, 1638, 1390, 1310, 1260, 1228, 1180, 1050, 1030.

Preparation of 8-isopropenyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-1-ol (28). Hydroxyketone (16b) (0.238g, 0.0012 mol.) was dried by azeotropic evaporation with toluene under reduced pressure. It was diluted with 4 ml of DMSO and preserved for later use.

Sodium hydride (3.8 eq. 0.218g, 50% emulsion) was weighed in a dry box and washed twice with 5 x 10 ml of dry pentane. After removal of pentane, 6.5 ml of DMSO was added. The mixture was stirred at 65-70°C for an hour while all hydrogen was generated and the solution became clear. The mixture was cooled down to 10°C and methyltriphenylphosphonium bromide in 6 ml of DMSO was introduced via syringe dropwise for 5 min. period. The reaction vessel was warmed to 30°C. for 15 min. and then cooled to 15°C. The previously prepared alcohol (16b) was injected via syringe slowly and the reaction mixture was stirred at room temperature overnight. It was quenched with 30 ml of water (mildly exothermic) and extracted with pentane (5 x 30 ml), and the organic layer was washed with brine, water and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica with 1/10 EtOAC/pentane to give a colorless oil as the product (28), 0.143g, 61% yield. NMR($CDCl_3$) δ 1.80 (s, 3H0, 1.95 (m, 12H), 2.80 (s, 1H), 3.40 (m, 1H), 4.89 (d, 2H), 5.51 (s, 1H); IR (neat), 2920, 2850, 1635, 1445, 1105, 1080, 878, 800; ^{13}C NMR, 152.6, 136,8, 121.4, 110.4, 75.2, 48.1, 47.5, 34.9, 34.2, 27.5, 24.2, 23.9, 18.7.

Preparation of 3-ethoxycyclohex-2-enone (29). Cyclohexadione (200g, 2.08 M) was placed in a 2000 ml round bottom flask with 1000 ml of dry ethanol. p-Toulene sulfonic acid (2g) was added. The reaction mixture was refluxed in an oil bath at 95°C for overnight. The vessel was cooled to room temperature, and ethanol was evaporated under reduced pressure. The residue was quenched with $NaHCO_3$ solution, extracted with 3 x 300 ml of Et_2O, washed with brine, dried over $MgSO_4$. It was concentrated under reduced pressure, and the residue was distilled through Vigreux column to produce a colorless liquid as the product; yield, 86%: NMR($CDCl_3$) δ 1.40 (t, 3H), 2.05 (m, 2H), 2.42 (m, 4H), 4.06 (q, 2H), 5.04 (s, 1H); MS m/e 140, 112, 95, 84, 68, 55, 43, 39, 28.

Preparation of 3-vinylcyclohex-2-enone (30). In a 2000 ml round bottom flask equipped with a mechanical stirring bar, was placed magnesium turnings (48.6q, 2.0 mol) with 1000 ml of dry THT. Vinylbromide (197g, 2.4 eq. 1.83 mol) was added via a 2-way needle by warming the vinyl bromide container slowly. After approximately 50g of vinyl bromide was transferred, 0.5g of iodine crystals were added. A few minutes later, reaction started spontaneously. After 20 min, the rest of vinyl bromide was added over a 2 hour period, and the reaction mixture was stirred for an additional 3 hours. Ethoxycyclohexenone (29) (140g, 1 mol) in 100 ml of ether was added for 10 min. period and stirred overnight at room temperature. This reaction mixture was quenched with $NaHCO_3$ solution, brine and dried over $MgSO_4$. The solvent was

evaporated under reduced pressure, and the crude product was used immediately for the reduction of ketone by Dibal-H. The product (30) polymerized quickly and was unstable at room temperature: 72% yield: NMR($CDCl_3$) δ 2.40 (m, 6H), 5.99 (m, 3H), 6.13 (s, 1H); IR (neat), 2990, 2975, 1654, 1450, 1444, 1385, 1250, 1110, 898, 878, 850; MS, m/e 122, 94, 80, 55, 41, 31, 29.

Preparation of 1-t-butyldimethylsiloxy-3-vinylcyclohex-2-ene (31). In a 50 ml round bottom flask, NaH (50% emulsion, 0.0011 mol, 1.3 eq. 0.050g) was placed, under N_2, and was washed with 2 x 3 ml of pentane. After pentane was decanted, 10 ml of THF was added and the temperature was lowered to 0°C. With 5 ml of THF, 0.10g (1 eq., 0.00086 mol) of alcohol (14) was introduced slowly over a 5 min. period. The reaction mixture was stirred at 0°C for 30 min. and TBDMSCl in 5 ml of THF was introduced via syringe. The reaction vessel was warmed to room temperature after 30 min. stirring at 0°C. The reaction mixture was quenched with water, extracted with 3 x 50 ml of ether, washed with brine, dried over Na_2SO_4. After evaporation of solvent under reduced pressure, the residue was chromatographed on 5 cm short silica column to produce a colorless oil as the product; yield, 0.170g, 83%: NMR($CDCl_3$) δ 0.85 (s, 6H), 0.87 (s, 9H), 1.58 (m, 4H), 2.01 (m, 2H), 4.29 (b.s. 1H), 5.60 (m, 4H); IR (neat), 3360, 2910, 1665, 1430, 1352, 1110, 990, 880; MS, m/e 239, 211, 202, 175, 124, 106, 96, 83, 69, 55, 41.

Preparation of 1-methylene-4a-methyl-8-carbethoxy octahydronaphthalene (32). Sodium hydride (0.302g, 50% emulsion, 0.0063 mol, 3 eq.) was placed in a 50 ml round bottom flask and washed with 2 x 5 ml of dry pentane. After removing pentane, 5 ml of DMSO was added and the mixture was stirred at 65-75°C for an hour until all hydrogen was generated and the solution became clear. The reaction vessel was cooled to 10°C and triphenylphosphonium bromide (2.25g, 0.0063 mol, 3 eq.) in 5 ml of DMSO was added via syringe dropwise over a 5 min. period. The reaction vessel was warmed to 30°C for 15 min. and cooled to 15°C. The previously prepared ketoester (26b) (0.50g, 0.0021 mol, 1 eq.) in 5 ml of DMSO was added via syringe over a 5 min. period and stirred at room temperature overnight. The reaction mixture was quenched iwth 20 ml of water (mildly exothermic) and the product was extracted with 5 x 50 ml of pentane, washed with brine, water and dried voer $MgSO_4$. The solvent was evaporated and the residue was chromatographed on 10g of silica (230-400 mesh) with 10/90 EtOAC/pentane to give a colorless oil as the product (32); yield, 53%, 0.262g: NMR($CDCl_3$) δ 0.92 (s, 3H), 1.08 (t, 3H), 1.58 (m, 9H), 2.07 (m, 4H): 2.75 (m, 1H), 4.10 (q, 2H), 4.68 (m, 2H); IR (neat), 2990, 1760, 1745, 1460, 1090, 1040, 945, 870, 860, MS, m/e 236, 221, 192, 160, 147, 133, 119, 104, 90, 76, 62, 48, 34.

Preparation of 1-methylene-4a-methyl-8-isopropenyl-decahydronaphthalene (34). The tertiary alcohol (33) (0.037 mg, 0.00017 mol) in dry pyridine (1.5 ml) was cooled to -15°C under N_2, and treated dropwise with freshly distilled $SOCl_2$ (0.12 ml, 0.014 mol). The reaction vessel was warmed to room temperature slowly for an hour period and stirred for additional 10 min. The reaction mixture was poured into ice, extracted with 4 x 25 ml of pentane, washed with 10% HCl, $NaHCO_3$ solution, brine, water and dried over $MgSO_4$. The crude product was chromatographed on silica (4g, 230-400 mesh) with 10:90 ether:pentane to give a colorless oil as the product; yield, 78%: NMR($CDCl_3$) δ 0.90 (s, 3H), 1.60 (m, 9H), 1.61 (s, 3H), 1.91 (m, 4H), 2.49 (m, 1H), 4.60 (m, 4H); ^{13}C NMR, 149.1, 148.9, 110.1, 109.3, 54.8, 45.2, 40.7, 34.6, 32.3, 30.2, 28.5, 23.4, 21.6, 17.8, 17.0.

Preparation of 8-isopropenyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-1-one (35). To a 50 ml 3-necked round bottom flaks, containing 0.95g (12 mmol) of pyridine in 15 ml of methylene chlroide, chromium trioxide (0.60g, 6 mmol) was added via a Birch tube slowly over a 5 min. period while stirring under N_2. The dark brownish solution was stirred for an additional 15 min. at room temperature. At the end of this period, a solution of the alcohol (28) was added with 3 ml of methylene chloride in one portion. After stirring 15 min. at room temperature, the reaction mixture was quenched with 5% NaOH solution, and extracted with 3 x 100 ml of ether. The organic layer was washed with 5% HCl solution,

$NaHCO_3$ saturated solution, brine, water and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica with 20/80 ether/pentane to produce a colorless oil as the product (35); yield 71%: NMR($CDCl_3$) δ 1.65 (m, 6H), 1.79 (s, 3H), 2.40 (m, 4H), 2.80 (m, 1H), 3.12 (m, 1H), 4.77 (d, 2H), 5.75 (b.s. 1H); IR (neat), 2915, 1715, 1640, 1450, 1432, 1310, 1255, 1050, 1010, 885. MS, m/e 190, 162, 149, 123, 120, 112, 98, 84, 71, 59, 54, 48, 33, 28.

Preparation of 2a,3a,4,6,7,8,8a,8b-octahydro-4-phenylsulfonyl-2H-naphtho(1,8-bc)furan-2-one (39). Sulfonyl ester (38) was prepared by the procedure of Strekowski. The ester (38) (0.10g, 0.00037 mol) in 20 ml of dry toluene was placed in a 50 ml round bottom flask, under Argon, equipped with a magentic stirring bar. A pinch (ca. 5 mg) of hydroquinone was added as a polymerization inhibitor. The reaction was heated at 110°C for 36 hours. The solvent was evaporated under reduced pressure and the residue was chromatographed with 50/50 EtOAC/pentane on silica (10g) (230-400 mesh) to give a brownish solid. The solid was not soluble in hexane, but slightly soluble in EtOAC. The pure product was obtained by recrystallization with $CHCl_3$ and hexane; yield, 63 mg, 58%. m.p.: 221-222°C: NMR($CDCl_3$) 300 MHz, δ 1.52 (m, 2H), 1.90 (m, 1H), 2.04 (m, 1H), 2.38 (m, 3H), 2.65 (m, 1H), 2.85 (m, 1H), 2.98 (m, 1H), 3.76 (m, 1H), 4.58 (m, 1H), 5.58 (s, 1H), 7.59 (m, 2H), 7.66 (m, 1H), 7.96 (m, 2H); IR (neat), 2988, 2910, 1770, 1642, 1440, 1338, 1340, 1288, 1270, 1265,

1200, 1280, 1125, 1040, 990, 920: MS, m/e 319, 177, 159, 131, 104, 91, 77, 65, 51, 39.

Preparation of 2a,3a,4,6,7,8,8a,8b-octahydro-4-carbethoxy-7,7-dimethyl-2H-naphtho(1,8-bc)furan-2-one (41). In a 250 ml round bottom flask, was placed the ester (40) (0.639g, 0.0023 mol) and 100 ml of dry toluene. Hydroquinone (10mg) was added and the reaction vessel heated at 110°C for 24 hours under N_2. After cooling to room temperature, toluene was evaporated under reduced pressure and the residue was chromatographed on a silica column (10g, 230-400 mesh) with 5/1 hexane/ether to give a colorless viscous oil as the product; yield; 356 mg, 71%. G.C. analysis showed 2 peaks with the ratio of 97:3; NMR($CDCl_3$) 300 MHz δ 1.00 (s, 3H), 1.10 (s, 3H), 1.15 (t, 3H), 1.40 (m, 1H), 1.78 (m, 1H), 2.00 (s, 2H), 2.40 (m, 1H), 2.74 (m, 4H), 4.22 (q, 2H), 4.72 (m, 1H), 5.38 (s, 1H); ^{13}C NMR, 173.8, 173.6, 137.4, 119.9, 76.3, 61.0, 42.8, 41.2, 39.4, 38.7, 32.0, 31.6, 30.7, 30.6, 14.1; MS, m/e 278, 260, 232, 217, 205, 199, 187, 159, 151, 145, 131, 117, 105, 97, 91, 89, 85, 81, 79, 77, 71, 69, 63, 57, 55, 51, 45, 43, 41, 39, 32, 29. High resolution MS cald for $C_{16}H_{22}O_4$ 278.1518, Found 278.1518.

Preparation of cyclohexa-1,4-diene epoxide (42). A solution of mCPBA (75.93g, 0.374 mol, 1.2 eq. 85%) in 1200 ml of CH_2Cl_2 was added to a solution of cyclohexadiene (25.0g, 0.312 mol, 1 eq.) in 200 ml of CH_2Cl_2 in a 2000 ml of round bottom flask. The temperature was maintainted between 20-30°C while stirring. The reaction mixture was

stirred for an additional 2 hours, whereupon excess peracid was destroyed by addition of 100 ml of 10% aqueous Na_2SO_3 solution. The mixture was washed with Na_2CO_3 solution, extracted with 3 x 200 ml of ether, washed with brine, water and dried over $MgSO_4$. After evaporation of the solvent, the product was distilled through a short column to give a white solid as the product (42) after cooling; yield, 89%: NMR($CDCl_3$) δ 2.45 (s, 4H), 3.20 (s, 2H), 5.45 (s, 2H); IR (neat) 2990, 2945, 2820, 1420, 1348, 1264, 1212; MS, m/e 96, 84, 67, 55, 39, 29.

Preparation of 2-(2'-oxopropyl)cyclohex-4-enol (43). In 2 25 ml 3 necked round bottom flask equipped with reflux condenser, there was placed 9.5 mg (3 eq.) of magnesium turnings and 5 ml of dry ether under Argon. Chloromethyltrimethylsilane (0.51 ml, 0.00362 mol) in 5 ml of diethyl ether was added and a small pinch of iodine was also added. After vigorous reaction ceased the reaction mixture was heated at 40°C for 2 hours. The reaction vessel contents were cooled to 0°C and the lactone (17) (0.186g, 0.0012 mol) in 5 ml of ether was introduced via syringe. It was allowed to warm up to room temperature slowly and stirred overnight. The reaction mixture was quenched with dilute HOAC and the product was extracted with 3 x 100 ml of ether, washed with $NaHCO_3$ solution, brine, water, and dried over $MgSO_4$: NMR($CDCl_3$) δ 2.10 (m, 8H), 2.15 (s, 3H), 3.50 (m, 1H), 5.61 (s, 2H); IR (neat), 3450, 3020, 2900, 2840, 1710, 1435, 1305, 1260, 1200, 1110, 1050 MS, m/e 154, 136, 108, 91, 78,

57, 55, 47. High resolution MS Calcd. for $C_9H_{14}O_2$ 154.0993, Found 154.0993.

Preparation of 2-(2'-hydroxy-2'-methyl,propylcyclohex-4-enol (44). In a 50 ml 3 necked round bottom flask, the lactone (17) (100 mg, 0.000724 mol) was dissolved in 5 ml of THF under N_2 and the temperature was lowered to 0° C. Methyllithium (3 eq., 1.6 M solution in ether, 0.00217 mol, 1.36 ml) was then added via syringe. The reaction vessel was warmed up to room temperature and stirred for additional 15 min. The reaction mixture was quenched with water, extracted with 3 x 30 ml of ether, and dried over $MgSO_4$. After evaporation of the solvent, the crude product was chromatographed on short silica column to produce a colorless viscous oil as the product; yield: 86 mg, 71%: NMR($CDCl_3$) 1.23 (s, 6H), 1.93 (m, 8H), 3.48 (m, 1H), 4.06 (m, 1H), 5.60 (s, 2H); IR (neat), 3260, 3020, 2985, 2900, 2840, 1465, 1433, 1360, 1075, 1045, 980, 905, 730, 660. MS, m/e 170, 155, 141, 135, 125, 117, 111, 105, 100, 97, 85, 81, 71, 69, 57. High resolution MS Calcd. for $C_{10}H_8O_2$ 170.1306. Found 170.1311.

Preparation of 2-isobutenylcyclohex-4-enol (51). In a 250 ml 3 necked round bottom flask, sodium hydride (0.195g, 1.1 eq., 80% emulsion, 0.0081 mol) was placed and washed with 3 x 5 ml of pentane. DMSO (10 ml) was added after the pentane was decanted. Methyltriphenylphosphonium bromide (2.850g, 0.0081 mol) was added with 10 ml of DMSO and the reaction mixture was stirred for 30 min., and the

hydroxyketone (43) (0.100g, 0.0040 mol) was added slowly over a 5 min. period. It was stirred at room temperature overnight and the reaction mixture quenched with water, extracted with 5 x 100 ml of pentane, washed with brine, water and dried over $MgSO_4$; yield, 69%: NMR($CDCl_3$) δ 1.70 (s, 3H), 2.00 (m, 7H), 2.42 (s, 1H), 3.60 (m, 1H), 4.72 (s, 2H), 5.58 (s, 2H); IR (neat), 3180, 3030, 3010, 2985, 2905, 1645, 1430, 1370, 1090, 1045, 885; MS, m/e 152, 134, 102, 94, 77, 65, 43, 28.

The 3,5-dinitrobenzoate derivative of (51) was obtained by treating alcohol (51) with 3,5-dinitrobenzoylchloride in pyridine at room temperature. Recrystallization from methanol gave the analytically pure material. Anal. Calcd. for $C_{17}H_8N_2O_6$; C 58.95, H 5.24. Found, C 59.00, H 5.24.

Preparation of 2-isobutenylcyclohex-4-enone (52). Chromium trioxide (0.60g, 0.0060 mol) was added to a magnetically stirred solution of 0.95g (0.012 mol) of pyridine in 20 ml of methylene chloride under N_2. The dark brownish solution was stirred for 15 min. at room temperature, and the alcohol (51) (0.10g, 0.0006 mol) was added in 5 ml of methylene chloride in one portion. After stirring an hour at room temperature, the reaction mixture was quenched with 5% NaOH aqueous solution. The product was extracted with 3 x 100 ml of ether, washed with 5% HCl, 5% $NaHCO_3$ solution, water and dried over $MgSO_4$. It was concentrated by vacuo and the crude product was chromatographed on silica with

15/85 ether/pentane to obtain a colorless oil as the product (52); 64% yield: NMR($CDCl_3$) δ 1.52 (s, 3H), 2.30 (m, 5H), 2.80 (s, 2H), 4.65 (m, 2H), 5.70 (s 2H); IR (neat), 3080, 3040, 2985, 2920, 1720, 1645, 1440, 1375, 1300, 1225, 1140, 890; MS, m/e 150, 135, 109, 81, 67, 53, 39.

Preparation of 2-isobutenylcyclohex-5-enone (53). Absolute ethanol (3 ml) was placed in a 10 ml round bottom flask and sodium (0.2g, 0.00870 mol) was added under N_2. After all hydrogen evolution ceased, the reaction vessel was cooled to room temperature, and the ketone (0.30g, 0.002 mol) in ethanol (2 ml) was added at room temperature in one portion. After 10 min., the reaction mixture was quenched with 5 ml of water, and most of alcohol was evaporated under reduced pressure. The product was extracted with 3 x 50 ml of ether, washed with brine, water and dried ($MgSO_4$) overnight. The solvent was evaporated under reduced pressure and the crude product was chromatographed on silica with 10/90 ether/hexane to give a colorless liquid as the product (53); yield, ca. quantitative: NMR($CDCl_3$) δ 1.74 (s. 3H), 2.25 (m, 7H), 4.75 (m, 2H), 6.06 (d, 1H), 7.02 (m, 1H); IR (neat), 3070, 3030, 2925, 1680, 1650, 1620, 1440, 1380, 1290, 1260, 1220, 1120, 890, 790, 760; MS, m/e 150, 135, 107, 95, 82, 68, 55, 39, 27. High resolution MS Calcd. for $C_{10}H_{14}O$ 150.1044, Found 150.1032.

Preparation of 2-methylene-2a,3,4,6,7,8,8a,8b-octahydro-2H-naphtho(1,9-bc)furan (57). Dicyclopentadienyl titano-2,2,-dimethylcyclobutene (60) was prepared by the procedure of Straus.[52] This cyclometallic compound was weighed (0.168g, 0.000674 mol) in a dry box and transferred to a 20 ml glass tube (reaction and storage tube with pressure and vacuum stopcock) and 10 ml of dry benzene was added via 2-way needle. This lactone (15a) (0.100g, 0.000562 mol) was added with 5 ml of dry benzene at room temperature and stirred for 20 min. The reaction was carried out under Argon. The reaction mixture was quenched with 20% NaOH solution, extracted with 3 x 100 ml of ether, washed with $NaHCO_3$ solution, brine, water and dried over $MgSO_4$. After evaporation of the solvent, the crude product was not purified further and was used directly for conversion to hemiketal (16c). Yield for (57) was 91%: NMR($CDCl_3$) δ 1.20 (m, 7H), 2.03 (m, 4H), 3.25 (m, 1H), 4.01 (m, 2H), 4.85 (m, 1H), 5.62 (m, 1H).

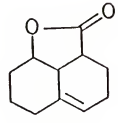
Preparation of 2a-methyl-3,4,6,7,8,8a,8b-octahydro-2H-naphtho-(1,8-bc)furan-2-one (58). In a 25 ml round bottom flask, diisopropylamine (0.087 ml, 1.1 eq., 0.000618 mol) was placed with 5 ml of THF under N_2. It was cooled to -78°C, and n-BuLi (0.25 ml, 1.1 eq., 0.000618 mol, 2.5 M solution in hexane) was added dropwise while stirring. The temperature was increased to 0°C and the reaction mixture stirred for 15 min. and cooled to -30°C. The lactone (15a) (0.100g, 0.000562 mol) was introduced and the mixture was

warmed to 0°C for 10 min. period and cooled to -10°C. Methyl iodide was added via syringe slowly over a 1 min. period and the reaction mixture was stirred for an additional 15 min. The reaction vessel was warmed to 0°C for a 20 min. period. It was quenched with $NaHCO_3$ saturated solution, extracted with 3 x 50 ml of ether washed with brine, water and dried over $MgSO_4$. Flash column chromatography on short silica column gave a light brownish viscous oil as the product; yield, 95%: NMR($CDCl_3$) δ 1.37 (s, 3H), 1.52 (m, 6H), 2.20 (m, 5H), 3.86 (m, 1H), 5.05 (m, 1H); IR (neat), 2988, 2910, 1775, 1610, 1226, 1220, 998, 990, 870.

Preparation of 8-isopropenyl-1,2,3,4,5,6,7,8-octahydronaphthalen-1-ol (65). In a 25 ml round bottom flask, 100 mg of ketone (27) (0.000526 mol) was placed with 5 ml of diethyl ether under N_2. The reaction vessel was cooled to 0°C and Dibal-H (1 M solution in hexane, 2 eq., 1.05 ml) was introduced slowly via syringe. The reaction mixture was stirred for 30 min. at 0°C and quenched with 10 ml of water and extracted with 5 x 30 ml of diethyl ether, washed with $NaHCO_3$ saturated solution, brine, water and dried over $MgSO_4$. After evaporation of solvent, the crude product was chromatographed on preparative thin layer plate (Silica, 2 mm, Kodak) with 20:80 diethyl ether:pentane. The product (65) was a colorless oil; yield, 84%: NMR($CDCl_3$) δ 1.60 (m, 7H), 1.83 (s, 3H), 1.95 (m, 6H), 2.71 (s, 1H), 3.98 (s, 1H), 4.79 s, 1H), 4.96 (s, 1H); IR (neat), 3478, 2895, 1662, 1638, 1454, 1268, 1178, 1070, 1045, 942, 896; MS, m/e 192, 174,

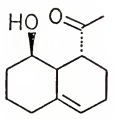
159, 145, 131, 117, 105, 91, 79, 67, 55, 41, 29. High resolution MS calcd. for $C_{13}H_{20}$: 192.1514; Found, 192.1505.

APPENDIX



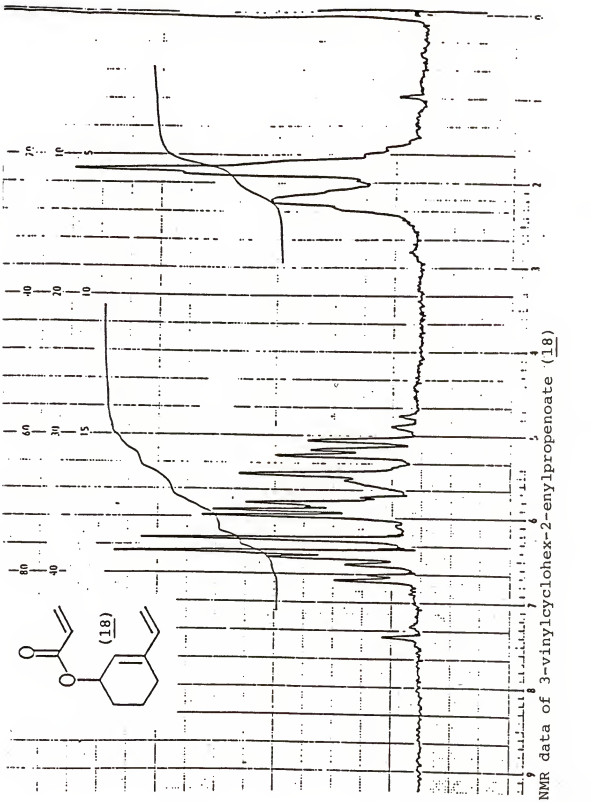
(15a)

NMR data of 2a,3,4,7,8,8a,8b-octahydro-2H-naphtho(1,9-bc)furan-2-one (15a)

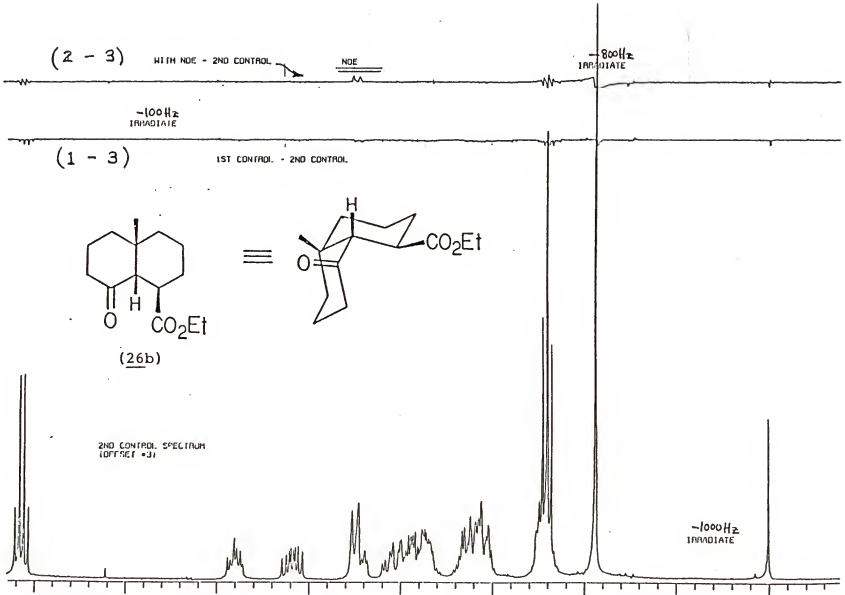


(16a)

NMR data of 1-hydroxy-8-acetyl-1,2,3,4,6,7,8,8a-octahydronaphthalene (16a)

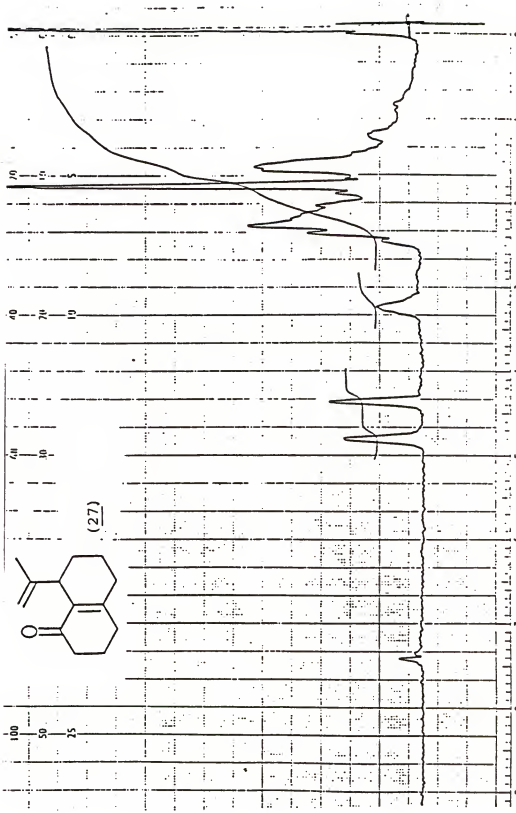


NMR data of 3-vinylcyclohex-2-enylpropenoate (18)

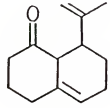


(26b)

NMR data of 4a-methyl-8-carbethoxy-1,2,3,4,5,6,7,8,8a-decahydronaphthalene-1-one (26b)

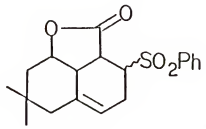


NMR data of 8-isopropenyl-1,2,3,4,5,6,7,8-octahydronaphthalen-1-one (27)



(35)

NMR data of 8-isopropenyl-1,2,3,4,6,7,8,8a-octahydronaphthalen-1-one (35)



(39)

NMR data of 2a,3a,4,6,7,8,8a-octahydro-4-phenylsulfoxy-2H-naphtho(1,8-bc)furan-2-one(39)

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BIOGRAPHICAL SKETCH

Sukbin (Ben) Kong was born on March 1, 1948, in Korea. He graduated from the High School of Seoul National University in 1965. He received his Bachelor of Science degree from Seoul National University majoring in plant pathology and entomology in 1970, and served as a junior government officer until he was called to military service. He also served in Vietnam from 1971 to 1972. After being discharged from the service in 1973, he worked as a junior researcher in the government and was employed by a brewery company until he came to America in 1975.

He received his master's degree from the Department of Entomology and Nematology in 1978, and received another Master's degree majoring in chemistry in 1983.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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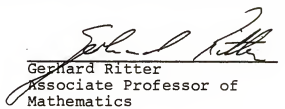

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This dissertation was submitted to the Graduate Faculty of the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December 1985

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